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Localized childhood Hodgkin's disease : response adapted treatment by chemotherapy (CT) regimen with VP16, Bleomycin, Vinblastin and Prednisone (VBVP) before low-dose radiation therapy (RT). Results of the study by the French Society of Pediatric Oncology (SFOP)

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Background : The first study of the SFOP demonstrated the effectiveness of 20 grays (Gy) in involved fields after initial CT (ABVD or MOPP/ABVD) (JCO, 10, 1992, 1602). In further attempt to reduce the long term side effects of therapy, in 1990, the SFOP initiated a new study based on CT devoid of both alkylating agents and anthracyclins for good responders.
Design : In clinical stage (CS) I and II, all the patients (pts) were given 4 cycles of VBVP : Vinblastin 6mg/m² days 1 and 8, Bleomycin 10mg/m² day 1, VP16 100mg/m² days 1 to 5, Prednisone 40mg/m² days 1 to 8. Cycles were repeated every 3 weeks. At completion of the fourth cycle, clinical evaluation was performed. Good responders were given 20 Gy to initially involved areas (+ lombosplenic field for CS IB and IIB). Poor responders were given OPPA (Vincristine 1,5mg/m², Procarbazine 100mg/m² days 1 to 15, Prednisone 60mg/m², Adriamycin 40mg/m² days 1 to 14). After new evaluation, good responder pts were given 20 Gy and poor responder pts were given 40 Gy.
Results : From january 1990 to july 1996, 207 pts (69% males) below 16 years of age from 27 centers were included. 179 pts have completed their therapy and are evaluable (69 IA, 89 IIA, 3 IB, 46 IIB). After 4 VBVP, 76pts (43%) achieved complete remission and 74 pts (42%) had a response >70%. They were given 20 Gy RT, with boost up to 40 Gy for 3 pts. 29 pts (15%) were considered as poor responders to VBVP and received one or two OPPA cycles : 11 pts achieved good response and received 20 Gy with localized boost up to 40 Gy for 4 pts. 12pts had a response < 70% and received 40 Gy on all involved areas (6/12) or 20 Gy with mediastinal boost up to 40 Gy for 6 pts. Six pts failed to respond, 3 of them died of uncontrolled disease, 3 are free of disease after HDCT and ABMT (58,45,24 months follow up)
Current median follow-up of the pts is 38 ± 18 months (6 to 78). The 38 months event free survival is 92% and overall survival 97%. 10 relapses occured (5 to 56 months) off which 9/10 are in second remission. One patient presented secondary leukemia (LAM5, MLL rearrangement neg), 1pt developed myelodysplasia after VBVPX4 + OPPA at 54 months. **Conclusion :** These results are encouraging and longer follow-up is needed. Nevertheless those data support that localized childhood Hodgkin's disease can be cured by CT devoid of alkylating agents and anthracyclins followed by low dose radiation therapy in good responders.

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LYMPHOPROLIFERATIVE DISEASE RELATED TO IMMUNOSUPPRESSION OR IMMUNODEFICIENCY. RESULTS OF THE UNITED KINGDOM CANCER STUDY GROUP REGISTRY 1994-1996 (UKCCSG STUDY 9404)

I Hann, R Pinkerton, R Gowing, D Kelly, M Burke, D Crawford & A Thomas on behalf of the Lymphoproliferative Disease Working Group of the United Kingdom Childrens Cancer Study Group (UKCCSG)

The UKCCSG 9404 study attempts to register all cases of lymphoproliferative disease (LPD) related to immune deficiency or immunosuppressive therapy and to obtain specimens for scientific study. Between October 1994 and February 1997 26 cases were reported, 18 following organ transplant (OT), 2 renal, 4 cardiac and 12 hepatic. 7 cases were associated with immunodeficiency following ALL, HIV (2 cases), common variable immune deficiency, ataxia-telangiectasia hypogamma and immunoblastic lymphoma. 8 tumours were localised, of these patients none have died. In 6 cases (1 died) the information on sites is as yet unavailable. The localised sites were cervical in 3, and one case each in the groin, axilla, iris and nasopharynx. All 12 (6 dead) disseminated tumours included peripheral nodal involvement with cervical nodes in all cases; the abdomen was involved in 5 and nasopharynx in 4. Central histology review is ongoing and so far 21 cases have been classified as: 12 polymorphous, 3 minimal polymorphous, 2 monomorphous and 4 unclassifiable. The OT cases comprised 10 males and 8 females aged 11 months to 17 years (Median 10 years). The onset of LPD was 2-63 months after OT, half occurring within 12 months.
Four of the 18 (22%) OT cases have died, only three having been given chemotherapy. 3 of the 7 non-OT cases have died, two are alive and in two cases data is missing. The cause of death was usually progressive LPD, but graft rejection contributed to death in several cases. The registry aims to define the natural history and aetiology of this severe disorder and identify patients requiring chemotherapy at an earlier stage.

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AIDS-RELATED LYMPHOMAS - RESULTS OF TREATMENT ACCORDING TO THE NHL-BFM-TRIALS.

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Non-Hodgkin´s lymphomas (NHL) with particular clinicopathological features are a typical complication of the aquired immundeficiency syndrome (AIDS). These lymphomas have more frequently an extranodal location. In comparison to other children with NHL, the decision for treatment bases on different concerns. The main concern is the stage of the underlying disease and adult prospective treatment trials report a higher hematologic toxicity of combination chemotherapy for patients with AIDS-related NHL.
We present the data of 7 patients treated for AIDS-related NHL according the NHL-BFM-protocol. All 7 patients had connatal HIV-infection. The mean age at diagnosis of NHL was 5,6 years (2,5 - 12 years). The stage of AIDS was : 5 patients stage C3, 1 patient had an asymptomatic reduction of the CD4 lymphocytes and 1 patient had lymphadenopathy, weight reduction and low CD4 counts, but no infections.
Immunology revealed that all NHLs were B-lineage derived. The histological distribution was: 3 Burkitt-lymphomas, 1 centroblastic/immunoblastic lymphoma and 3 are not histologically classified B-lymphomas.The patients had no blasts in the cerebrospinal fluid, one patient had bone marrow involvement (2% blasts).
Treatment results: All patients responded to therapy: 5 patients achieved CR, while 2 patients achieved PR after one chemotherapy cycle.
3 patients are still alive and in CCR. One patient died in PR after the first chemotherapy cycle of septic complications. One patient could not continue therapy because of detoriation of his AIDS-related cerebral situation. One patient finally died in CCR related to recurrent VZV infections 2 years after the end of therapy. One patient had a CNS-relapse 1 year after cessation of therapy and died.
The therapy-toxicity was increased (hematologic toxicity was WHO 3-4 after every cycle, and stomatitis WHO 3-4 after every HD-MTX).
The analysis of our few data shows, that a curative treatment of AIDS-related NHL is possible. We want to encourage to include patients with AIDS-related NHL in prospective trials especially in view of new antiviral agents.

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CA 125 LEVELS IN CHILDREN WITH NON-HODGKIN'S LYMPHOMA

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Objective: To evaluate the role of serum CA 125 levels for the diagnosis, follow-up and prognosis in childhood non-Hodgkin's lymphomas (NHL).
Patients and methods: Thirty-three children (median age 6 years, M/F

ratio 2.6) with NHL were included in this study. CA 125 levels in serum and/or ascitis, effusions were measured by RIA. The normal limit was 35 IU/ml. The correlation of CA 125 levels with tumoral location and treatment results was investigated.

Results: 23 (72%) patients (pts) had increased and 10 pts had normal serum CA 125 levels. 12 pts with increased CA 125 levels had malignant ascitis, pleural effusion or both, although none with normal CA 125 levels had any serous membrane involvement. The mean CA 125 levels were 75.6, 124.7, 227.9, 324.3 IU/ml in pts with no serousal involvement (no ascitis or effusion), pleural effusion, ascitis, ascitis+effusion respectively. CA 125 levels in ascitis and pleural effusion were 202.1 and 156.2 IU/ml respectively and similar to the corresponding serum levels ($p>0.05$). The increased CA 125 levels returned to normal in 14 pts whose diseases were in remission during the follow-up. Six (26%) out of 23 of pts with increased CA 125 levels died of progressive disease. Only one (10%) of 10 pts with normal CA 125 levels died of progressive disease.

Conclusion: CA 125 levels were found significantly higher in pts with serous membrane involvement and there was a correlation between treatment response and marker levels. Little is known for the expression in NHL. This is the first report in childhood NHL, suggesting that CA 125 levels can be used as an adjunctive factor for the diagnosis and follow-up of these patients.

O-139

TREATMENT OF CHILDHOOD LYMPHOBLASTIC LYMPHOMAS. RESULTS OF THE SFOP LMT 89 PROTOCOL (Société Française d'Oncologie Pédiatrique)

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Lymphoblastic lymphomas(LL) comprise about one third of the cases of childhood NHL. They are T or earlypreB in immunology. We report the results of SFOP LMT89 protocole for LL.

Patients and methods: the LMT89 protocol is a modified LMT81(MPO, 20: 105-113, 1992) with a new induction treatment : 1 course of COP[Cyclophosphamide (CPM) : 300 mg/m2 at D1, Vincristine and prednisone] and 2 courses of COPADM [CPM : 500 mg/m2 daily X 3, Adriamycine (AD) : 60 mg/m2 at D2, HDMTX: 3 g/m2, Vincristine and prednisone]. CCNU was removed, and 5 courses of Etoposide were added. The length of treatment was 1 year and we added 1 year more (MTX and 6-mercapto-purine) fort stages (st.) IV and acute lymphoblastic leukemia. We have done the same CNS prophylaxis than LMT81. 88 pts (54 boys and 34 girls) were included from 14 different SFOP centers from july 89 to may 96. Mean age was 10 years (0-17).

Results: 73 pts had mediastinal involvement, 4 pts had mediastinal, peripheral nodes and Waldeyer'ring involvement, and 11 pts had other sites. According to Murphy's staging we found 2 st.I, 3 st.II, 39 st.III; 19 St.IV and 25 acute lymphoblastic leukemia (all) (6 CNS+ ; 7 CNS+/BM+ and 31 BM+). 13/38 BM+ had less than 25 % blasts in BM, 25/38 had more than 25. The median follow up was 56 months (9-90). 24 events appeared : 2 partial remissions, 1 toxic death and 21 relapses (1 st I, 9 st III, 5st IV et 6 all). The rate of CR was 96%. 10/21 relapses were localize (1 alone and 9 combined with BM and CNS). 7/21 pts had CNS relapses (3 st. III, 2 st. IVCNS+, 2 all) ; 4/7 were CNS relapse alone, 1/7 was CNS with local relapse and 2/7 were CNS with BM relapse. BM was involved in 14/21 relapses.

	All pts (n=88)	I, II, III (n=44)	IV / all (n=44)	CNS+(n=13)
pEFS	69%±9	71%±13	69%±14	75%±25
pOS	79%±7	77%±13	80%±12	
Last event	48 (months)	31 (months)	48 (months)	15 (months)

Conclusions: Feasability and tolerance were acceptable. 3 CNS relapses in localized lymphoblastic lymphomas (stage III)(versus 0 in LMT81) is a high incidence and questions about schedule(pulse) of our induction phase. 7/21 relapses are in CR2 with a follow up time from 1.5 year to 4 years. The pEFS is slightly lower than LMT81 without statistically significativity. Probably, the pulse therapy is not appropriate for these lymphomas and we planed a come back to a sequential induction phase for the next protocol.

O-140

OUTCOME OF ADVANCED STAGE (III-IV) LYMPHOBLASTIC NON HODGKIN'S LYMPHOMA - A PEDIATRIC ONCOLOGY GROUP (POG) STUDY.

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In an effort to improve therapeutic outcome, POG embarked on T-cell immunophenotype-specific chemotherapy in the late 80's. Patients with advanced stage III/IV lymphoblastic NHL form the basis of this report.

Patients and Methods: Between May 1987 and January 1992, 226/250 eligible patients with Stage III-IV NHL were enrolled on POG 8691/8704. There were 161 males and 65 females with a median age of 10.3 yrs (6.1-14.0), median WBC at presentation of 7.7 x 10^9/l (5.0-10.7), and median LDH of 539 (321-920). 24 patients had CNS involvement. Patients were randomized to receive high dose (25,000u/m²) intensive asparaginase weekly for 20 weeks during consolidation. Treatment consisted of Induction, Consolidation and Continuation therapy of ten standard antileukemic drugs designed on an Ara-C backbone. The duration of therapy was 2 years. Central nervous system prophylaxis consisted of triple intrathecal therapy (MTX/HDC/Ara-C) only. Craniospinal radiation was given only to patients with CNS disease.

Results: 215/226 patients (95.1%) achieved CR. Five year CCR rates by treatment are 62% (SE=6%) on the control arm and 76% (SE=5%) on the L-ASP arm We conducted two forward stepwise Cox multivariate analyses, the first employing EFS as the dependent variable with independent variables gender, stage (3 vs 4), CNS involvement, LDH (subdivided at 500 and 1000), White Count (subdivided at 10), platelets (subdivided at 250), marrow involvement, race and primary site while the second utilized complete continuous remission (CCR) and added treatment group (which was randomized on 8704 after achievement of a CR). The only variable achieving statistical significance ($P<.05$) in either analysis was treatment favoring the L-Asparaginase arm ($P=.037$ two-sided).

Conclusions: With the exception of treatment, we were not able to find any major differences in outcome, when analyzed by any of the subgroups defined by our prognostic variables. As EFS improves, the prognostic importance of treatment risk factors diminishes and concern(s) relating to acute toxicities and adverse late sequelae increase.

O-141

RISK-ADAPTED THERAPY FOR LYMPHOBLASTIC T-CELL LYMPHOMA: RESULTS FROM TRIALS NHL-BFM 86 AND 90.

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Among 647 patients (pts) enrolled in two subsequent multicenter trials NHL-BFM 86 and NHL-BFM 90 53 and 101 patients, respectively, with a median age of 8.54 years (range 0.6-16.6y) were diagnosed with lymphoblastic T-cell lymphoma (LB-T NHL). The male to female ratio was 3:1. Pts were stratified according to clinical stage (St. Jude): Stage I (n=2), and stage II (n=3) for standard risk (SRG); stage III (n=119), and stage IV (n=30) for risk group (RG). 7 pts (4.5%) presented with initial CNS disease. Treatment was based on the ALL-BFM treatment regimen with a 8-drug induction (10 weeks), extracompartment consolidation with high-dose methotrexate (5g/m²x4; 8 weeks), and maintenance therapy (up to 24 months from diagnosis). Pts with stage III/IV LB-T NHL received in addition reinduction therapy (7 weeks). Prophylactic cranial irradiation was performed in RG only with 12 Gy (CNS+ pts: 24 Gy). Pts with incomplete response after induction were eligible for local radiotherapy. 149 pts (96.8%) achieved remission: 3 pts died due to early complications, 2 pts had resistant disease. 1 toxic death and 13 relapses (8.4%) were observed that with one exception occurred only among pts with advanced disease: There were 6 local, 2 isolated BM, and 4 combined local/BM relapses, but only 1 with CNS involvement. Second malignancies were

not observed. As of Oct. 1996, the probability for event-free survival (pEFS) for the total group of LB-T lymphoma is 0.87 (SE 0.03) after a median observation time of 4.3 years. pEFS for stage III is 0.87 (SE 0.03), and for stage IV 0.90 (SE 0.06). pEFS in trial NHL-BFM 86 is 0.79 (SE 0.06) compared to 0.92 (SE 0.03) in trial NHL-BFM 90. Thus, risk-adapted, ALL-oriented treatment of LB-T NHL can provide long-term EFS for approximately 90% of the patients.

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A SHORT-PULSE CHEMOTHERAPY IS AN EFFICACIOUS TREATMENT FOR ANAPLASTIC LARGE CELL LYMPHOMA (ALCL) OF CHILDHOOD: - A REPORT OF THE GERMAN-AUSTRIAN-SWISS TRIAL NHL-BFM 90

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In study NHL-BFM 90 we investigated the efficacy for treatment of patients (pts) with ALCL of a short-puls chemotherapy, originally designed for treatment of pts with B-cell neoplasias. Treatment was stratified into 3 branches: K1, stage (St. Jude) I, and II-completely resected; K2, stage II-not resected, stage III; K3, stage IV or multifocal bone disease. Two alternating 5-day courses of steroids, oxazaphorins, methotrexate (0.5 g/m^2 in K1+K2, 5 g/m^2 in K3), ARA-C, etoposide, doxorubicin, and i.th. therapy were given to a total of 3 courses in branch K1, and 6 in K2 and K3. In K3 two of the 6 courses were based upon HD-ARA-C/etoposide. From 4/90 to 3/1995, 87 evaluable pts with ALCL (age 0.8-16.9 y) were enrolled. The immunophenotype was T in 37 pts, B in 4, non-B/nonT in 31, histiocytic in 2, and not available in 13 pts. 8 pts had stage I, 20 stage II, 54 stage III, and 5 stage IV. Extranodal sites were: BM in 2 pts, CNS in 1, bone in 14, soft tissue in 13, skin in 15, lung in 12. 9 pts had splenomegaly, 21 hepatomegaly, and 44 had B symptoms. 28 pts had a mediastinal mass. 8 pts were treated in branch K1, 62 in K2, 17 in K3. pEFS at 5 years is .77 (SE .05) (Nov. 1st. 1996). Events were: 19 tumor failures, (15 in K2, 4 in K3); 1 second malignancy. Two failures occurred on therapy, 17 within 9 months off therapy. Sites of failure were: local in 9 pts, new sites in 4, local and new sites in 5, CNS in 1. Skin involvement and T-cell phenotype were associated with increased risk for failure ($p< 0.5$). Our results confirm that an intensive short-pulse therapy is an effective treatment for ALCL of childhood. Important issues, however, remain to be investigated in large controlled trials, e.g. appropriate stratification of treatment intensity and duration, and possible role of local therapy.

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ANAPLASTIC LARGE CELL LYMPHOMA IN CHILDREN : ANALYSIS OF 63 PATIENTS ENROLLED IN TWO CONSECUTIVE STUDIES OF THE SFOP

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Objectives : To investigate the efficacy of two consecutive regimens designed by the French Society of Pediatric Oncology (SFOP) for children with anaplastic large cell lymphoma (ALCL) and to identify prognostic factors in these children.

Patients and methods : Between 1989 and 1996, 68 children (median age 9 years) with ALCL confirmed histologically after central review of the slides were enrolled in two consecutive studies HM89 and HM91. According to the Ann Arbor classification there were 7 stage I, 16 stage II, 7 stage III and 38 stage IV. After a cytoreductive phase (vincristine, cyclophosphamide and prednisone), 2 induction courses with high dose methotrexate, cyclophosphamide, doxorubicin, vincristine and prednisone were administered. Maintenance treatment consisted of 8 alternate courses of VEM (methotrexate, VP16 and cyclophosphamide) and VAD (vincristine, doxorubicin) for HM89 and 8 alternate courses of VEBBP (vinblastine, etoposide, bleomycin, prednisone) and sequence 1 (methotrexate, cyclophosphamide, doxorubicin and prednisone) for the HM91 protocol. Length of the treatment was 7 to 8 months.

Results : 63 pts (92 %) achieved a CR. Three patients failed to achieve CR and died. 20 patients relapsed within 49 months after diagnosis (median 10 months). The probability of survival and event free survival at 3 years are respectively of 80 % (± 11) and 60 % (± 12). In a multivariate analysis, skin, lung and mediastinal involvement were shown to be predictive of a higher risk of failure.

Conclusion : This type of regimens demonstrates efficacy in children with ALCL without adverse prognostic factors. Children with lung, mediastinal or skin involvement should be treated more heavily.

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A NEW PROTOCOL FOR TREATMENT OF MATURE B-CELL LYMPHOMA/LEUKAEMIA (BCLL): FAB LMB 96, A SFOP LMB 96/CCG-5961/UKCCSG NHL 9600 INTERNATIONAL COOPERATIVE STUDY

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The prognosis for children with mature BCLL has improved dramatically over the past decade, with risk-adapted therapy and shorter, more intensive Tx for children with high risk features. SFOP has conducted 4 consecutive studies including LMB 0181, 84, 86, and recently, 89 (Patte et al *ASCO* 11:340, 1164, 1992). CCG recently concluded a pilot study comparing 2 short intensive Tx (Orange [Or] vs. LMB 89 Reg C [Fr]) in the treatment of disseminated childhood (stage III and IV) non-lymphoblastic NHL (Cairo et al *ASCO* 15:431, 1996). UKCCSG, utilizing LMB 89 has concluded two pilot studies: UK 9002 for stage III and CNS$^-$, stage IV and UK 9003 for BM and/or CNS$^+$ (Pinkerton et al, personal communication). In order to evaluate, on an international level, the long term EFS of short but intense therapy and to reduce acute toxicity and long term cardio-toxicity, impaired fertility, and secondary malignancy, SFOP, CCG, UKCCSG developed this international trial. In April 1996, FAB LMB 96 was opened with the specific aims to confirm the excellent EFS of LMB 89 Group (Gr.) A patients, to verify that the EFS is not substantially decreased when reducing LMB 89 Gr. B treatment by randomizing to a reduction in cyclophosphamide and/or a decrease in maintenance therapy, and to verify that EFS is not significantly decreased by randomly reducing the doses of CYVE and eliminating the last 3 courses of maintenance treatment. Patients with CNS$^+$ (Gr. C) will have CNS Xrt deleted and replaced by additional HD IV MTX and IT MTX. To date, 112 patients (10–Gr. A, 73–Gr. B, 28–Gr. C) have been entered on the international cooperative trial. It is estimated that over 90% of children treated on this mature BCLL trial will be cured of their disease.

*Each author contributed equally to this study and should be considered as primary authors.

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TREATMENT RESULTS FOR B-CELL LYMPHOMAS (B-NHL) AND ACUTE B-CELL LEUKEMIA (B-ALL) IN THE GERMAN-AUSTRIAN-SWISS STUDY NHL-BFM 90 - A REPORT OF THE BFM GROUP

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We investigated the efficacy of a short therapy for patients (pts) with B-NHL/B-ALL stratified by resectability, serum LDH concentration, BM-, or CNS-involvement, and initial response. Treatment was stratified into 3 risk groups: R1: completely resected, R2: unresected, extraabdominal only or abdominal and LDH < 500 U/L; R3: abdominal tumor and LDH ≥ 500 U/L, or BM+ or/and CNS+. After a cytoreductive prephase, pts received alternating 5-day therapy courses based upon MTX, oxazaphorins, etoposide, doxorubicin, steroids, and i.th. therapy up to a total of 2, 4, 6, in risk group R1, R2, R3, respectively. CNS pos. pts received intraventricularly applied therapy. Pts of risk groups R2 and R3 with incomplete response after 2 courses received an intensification based upon high HD-Ara-C/etoposide. Pts with no residual or necrotic residual tumor after intensification received 3 more therapy courses; those with viable tumor received autologous BMT. Radiotherapy was not used. From 4/1990 to 3/1995, 413 evaluable pts up to an age of 18 y with B-NHL/B-ALL were enrolled. As of Nov. 1st, 1996, pEFS at 6 years is .89±.02. The distribution of pts and pEFS by risk groups and stages (St. Jude) is given in the table. 8 pts received ABMT.

Stage		I	II	III	IV	B-ALL	total	pEFS
Risk	R1	27	41	2	0	0	70	1.00
group	R2	22	72	70	0	0	164	.94 (.02)
	R3	0	1	99	23	56	179	.81 (.03)
total		49	114	171	23	56	413	.89 (.02)
pEFS	(SE)	.95(.05)	.98(.01)	.86(.03)	83(.08)	.76(.08)		

Events were: death < day 8, 3; tumor failure, 26; second malignancy, 1; toxic death, 3 in R2, 8 in R3;. The incidence of toxic death was reduced after de-intensification of the cytoreductive prephase. We conclude, this treatment provides children with B-NHL/B-ALL a high chance for cure; the stratification system proved to be appropriate to adapt treatment intensity to the patients risk for failure; toxic death must be reduced for further improvement of results.

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DIFFUSE LARGE B-CELL LYMPHOMAS IN CHILDHOOD AND ADOLESCENCE: FAVORABLE OUTCOME WITH A BURKITT'S LYMPHOMA DIRECTED THERAPY IN TRIAL NHL-BFM 90-A REPORT OF THE BFM GROUP.

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The incidence of diffuse large B-cell lymphoma (DLBCL) as classified in the REAL-Classification is comparatively low in childhood and adolescence. Optimal treatment of DLBCL is not well defined up to now. In the NHL-BFM trials, patients with DLBCL were treated in the strategic arm for Burkitt's lymphoma. We analyzed patients with DLBCL entered into trial NHL-BFM 90 with respect to the pattern of clinical presentation and outcome. From 04/1990 to 03/1995, 56 of 645 patients (8.7%), 25 girls and 31 boys, with a mean age of 10.8 years (3.2-17.9) were diagnosed as DLBCL. According to the Kiel-Classification, 42 patients had centroblastic lymphoma (CBL), 6 immunoblastic lymphoma (IBL) and 8 mediastinal large B-cell lymphoma with sclerosis (MLBL). Clinical presentation and distribution of stages according to Murphy in correlation to the subentities:

	MEDIASTINE	BONE	SOFT TISSUE	SKIN	BM	CNS	STAGE I	STAGE II	STAGE III	ALL	EVENTS
CBL	6	1	2	0	0	0	14	17	11	42	2 rel.
IBL	1	0	0	0	0	0	0	2	4	6	0
MLBL	8	0	1	0	0	0	0	0	8	8	1 non resp.

4 patients with anaplastic large cell lymphoma of B-cell type were excluded.
Therapy was stratified into three branches: R1: completely resected; R2: not resected, abdominal primary and LDH < 500U/L; R3: abdominal primary and LDH ≥ 500U/L, cns or bone marrow involvement. Two alternating courses were given for a total number of 2, 4 and 6 in R1,2 and 3 respectively. Course 1: dexamethasone: 10mg/m²/d d1-5; vincristin: 1,5mg/m² d1; Vp16: 100mg/m²/d d4,5; Ara-C: 2x150mg/m²/d d4,5; methotrexate: 5g/m²/24h(500mg/m²/24h in R1)d1, Ifosfamid: 800mg/m²/d d1-5. Course 2: dexamethason: 10mg/m²/d d1-5; vincristin: 1,5mg/m² d1; adriamycin: 25mg/m²/d d4,5; methotrexate: 5g/m²/24h (500mg/m²/24h in R1) d1; cyklophosphamide: 200mg/m²/d d1-5. Patients with incomplete responses after 2 cykles received an intensification course consisting of dexamethason: 20mg/m²/d d1-5; vindesin: 3mg/m² d1; HD-AraC: 2x2g/m²/d d1,2; Vp16: 150mg/m²/d d3,4,5. Intrathekal triple therapy was given prophylactically in all courses. Patients with viable residuals after intensification were to undergo high dose chemotherapy with autologous stem cell rescue. As of Nov.1st. 1996, the probability for event free survival at 6 years is 0.94 (SE 0.3). We conclude, that the pattern of clinical presentation differs from that of ALCL by the paucity of skin, soft tissue and bone involvement and from that in Burkitt's lymphomas by the lack of bm or cns disease. The successful treatment regimen for Burkitt type lymphomas shows high efficacy also in DLBCL.

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RESULTS OF THE LMB 89 PROTOCOL FOR CHILDHOOD B-CELL LYMPHOMA AND LEUKEMIA (ALL). Study of the SFOP (French Pediatric Oncology Society)

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In the SFOP LMB 89 study, treatment (Tt) intensity was adapted to 3 risk groups : in group (gr) A (resected st I and abdominal st II), 2 polychemotherapy courses without CNS prophylaxis ; In group B (other st I and II, st III, st IV and ALL with bone marrow (BM) involvement < 70 %), 5 courses during 4 months (m) based on high dose (HD) methotrexate (MTX) (3 g/m²), cyclophosphamide and continuous infusion of Ara-C. In gr C (> 70 % blasts in BM and/or with CNS involvement), 8 courses during 7 m based on HD MTX (8 g/m²), triple intrathecal injections and with HD Ara C and VP 16. 24 Gy cranial irradiation was performed in case of CNS involvement.

566 evaluable pts were treated in 39 French, Dutch and Belgian centers from July 1989 to May 1996. Median age was 8 years and sex ratio was 3/1. The majority were classified as Burkitt. There were 34 st I, 88 st II, 279 st III, 63 st IV and 102 B-ALL. 67 had initial CNS involvement, 44 associated to BM involvement. Primary sites were : abdomen in 333, head and neck in 99, nodes in 35, elsewhere in 47. LDH level (known in 523 pts) was less and more than twice the normal in 263 and 260 pts respectively.

52 pts were treated in gr A, 391 in gr B, 123 in gr C. There were 18 early toxic or tumoral failures and 26 relapses 3 to 32 months (median : 5) after the beginning of Tt. 3 second malignancies occured later than 45 m. With a median follow-up of 48 m, 3 year EFS is 92 % ± 2 for all pts, 98 % ± 5 in group A, 92 % ± 2,5 in group B, 86 % ± 7 in group C, 96 % ± 3 in st I and II pts, 93 % ± 3 in st III, 88 % ± 4 in st IV and ALL, 79 % for pts with intial CNS involvement.

In conclusion, high cure rate was achieved in childhood B-cell malignancies with this short intensive risk adapted Tt. Possibility to decrease further Tt will be evaluated in a next study. *(supported by ARC, Villejuif, France).*

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ADDITIONAL CHEMOTHERAPY AGENTS IMPROVE TREATMENT OUTCOME FOR CHILDREN AND YOUNG ADULTS WITH B-CELL LYMPHOMAS.

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A short duration treatment protocol for children and young adults (up to 30 years) with SNC and DLC B-cell lymphomas was designed to determine whether additional agents would improve outcome. This protocol consisted of two chemotherapy regimens; A, used formerly, included CPM, DOX, VCR, and high dose MTX, and B, a new regimen included IFOS, ETOP and high dose cytarabine. Two alternating cycles of each regimen were given to high risk patients (a total of 4 cycles) and 3 cycles of regimen A to low risk patients. All patients received IT cytarabine and MTX. Since 1994, all

patients have received G-CSF. To date, 75 patients with SNCC (57) or DLC (18) lymphomas have been entered on study. There were 59 males and 16 females. The age range was 3 - 27 years (median, 14 years). Low risk patients had a single extra-abdominal mass or a small, completely resected intra-abdominal tumor with LDH < 350 (20). All other patients were high risk (55). To date 70 patients have achieved CR (2 subsequently relapsed) and 5, PR. EFS is 89% at 1 year and beyond. The median follow up is 33 months for patients who remained in CR. Neutropenia was documented in 94% of A cycles and 98% of B cycles. Infection was documented in 40% of A cycles and 56% of B cycles. Sepsis occurred in 17 % of A cycles and 27% of B cycles. There have been 2 toxic deaths, both from neutropenic colitis. The EFS rate in this protocol is significantly improved when compared to an earlier longer duration regimen, protocol 7704 (55%), suggesting that the additional drugs were beneficial, and 3 cycles for low risk patients and 4 cycles for high risk patients are sufficient. A risk-adapted treatment protocol focused on reduction of toxicity and earlier therapeutic modification in patients with partially responsive disease is planned.

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INTRAVENTRICULARLY APPLIED CHEMOTHERAPY AND INTENSIVE SYSTEMIC THERAPY IS EFFECTIVE FOR CNS POSITIVE PATIENTS WITH BURKITT-TYPE LYMPHOMAS OR ACUTE B-CELL LEUKEMIA (B-ALL).

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In trial NHL-BFM 90 we investigated the efficacy of intraventricularly (i.vent.) applied chemotherapy in combination with high-dose (HD) intravenous (i.v.) methotrexate (MTX) therapy for CNS pos patients with Burkitt-type lymphomas (BL) and B-ALL. From 4/90 - 3/95 30 pts (17 B-ALL, 13 BL) with CNS disease were registered. The diagnosis of CNS disease was based upon FAB-L3 blasts in the CSF in 21 pts, an intracerebral mass in 2 pts, cranial nerve palsy in 7 pts. Pts. received 2 alternating 5-day courses of therapy up to a total of 6. Course AA: vincristine, dexamethasone (DEXA), ifosfamide, cytarabine (Ara-C), etoposide (VP16), MTX 5 g/m²/24h. Course BB: DEXA, cyclophosphamide, doxorubicin, MTX 5 g/m²/24h. 6 pts with incomplete resolution of local tumors after the first 2 courses of therapy received course CC (DEXA, Vindesine, HD-Ara-C 2 g/m² q12h x 4, VP16) for course no. 3 and 6. Intrathecal MTX (12 mg), Ara-C (30 mg), and prednisolone (Pred) (10 mg) were given via lumbar puncture on day 1 and in two subdivided doses in the first course AA. During courses 2-6 MTX (3 mg) and Pred (2.5 mg) were given i.vent. via Ommaya reservoir on 4 consecutive days followed by one dose of Ara-C (30 mg) on day 5. No radiotherapy was used. 6 pts were excluded from analysis since i.vent. therapy was not given (5 pts, 3 suffered from CNS-relapse) or cranial radiotherapy was performed (1pt, 1 CCR). For the 24 protocol pts the Kaplan Meier estimates for a 4-year event free and disease free survival are 0.72 (SE 0.09), and 0.85 (SE 0.08), respectively (median follow-up 3.2 [0.4 - 5.8] years). One patient died of renal failure at day 8, 3 pts died of infection after the first course before an Ommaya reservoir was implanted. 3 pts suffered from relapse (CNS 1; BM 1; testes 1). No child suffered a major adverse event attributable to the Ommaya reservoir or i.vent. chemotherapy. We conclude, i.vent. applied fractionated chemotherapy combined with i.v. HD-MTX ± HD-Ara-C is a safe and effective treatment for pts with BL/B-ALL who have overt CNS disease at diagnosis.

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BURKITT'S LYMPHOMA IN CHILDHOOD: THE NORTHERN ISRAEL ONCOLOGY CENTER EXPERIENCE

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Sixty-eight patients (pts) median age: 5 years (y)range: 3-19 y; males:47, females:21, ratio:2.3:1 were diagnosed with Burkitt's Lymphoma (BL) from 1970 to 1995. Ethnic distribution-Arab:33, Jew:35. The abdomen(ABL) was the primary organ involved in 48 pts and the nasopharynx(NABL) in 16 pts, with other sites in 4 pts. Stage I-II were found in 28 pts (41%) and stages III-IV in 40 pts (59%). Initial treatment was chemotherapy (CT) in 27 pts (39%), surgery (S)+ CT in 33 pts (48%) and radiation therapy in addition to S or CT in 8 pts. Prior to 1985, pts were treated as follows: 22 pts received the COMP combination, 8 pts received the LSA2L2 combination, 4 pts received cyclophosphamide and vincristin, and 6 pts received single agent protocols. After 1985, all the pts- 10 with Stages I and II, and 18 with Stages III and IV - received CT according to the LMB protocol. Four pts underwent autologous bone marrow transplantation for local and/or distant recurrence (3 pts are cured). The overall 2 year survival is 65%, significantly higher in pts with Stages I-II compared to those with stages III-IV, 81% and 71%, respectively, and for pts diagnosed after 1985 as compared to those diagnosed prior to 1985, 86% vs 55%. After 1985, the 2 year survival for pts with Stages I-II is 100% and 76% for pts with Stages III-IV. Early diagnosis and an agressive approach in advanced stages are mandatory for the successful treatment of BL.

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OUTCOME OF 467 CHILDREN WITH DISSEMINATED SMALL NON-CLEAVED LYMPHOMA (SNCL) OVER AN 18 YEAR PERIOD: IMPROVED SURVIVAL WITH SHORT INTENSIVE THERAPY

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From 1977 to 1995, CCG conducted a series of 5 NHL clinical trials in which 467 pts had SNCL by institutional and central pathology review. Median age at diagnosis was 8 yrs (range 0-21 yrs); M/F (368/99). 467 had disseminated disease (DD); 54 of these 467 pts had CNS involvement, and 102 had BM disease (22 M2, 80 M3). The first trial, CCG-551 (1977-83) had 131 pts with DD who received 18 mo of COMP or LSA_2L_2. Thereafter, CCG-503, -552, and -5911 enrolled only pts with DD. On CCG-503 (1983-90), pts received COMP with (N=154) or without (N=84) doxorubicin for 18 mo. CCG-552 (1986-89) was a single arm pilot study which employed 10 mo of CHOP plus Ara-C, 6-TG, and VP-16 (N=52). CCG-5911 (1991-94) utilized short (6 mo) but intensive chemotherapy; pts were randomized to receive a CCG hybrid regimen (Orange, N=19) vs. the French LMB-89 regimen (N=24). Pts with DD SNCL treated on earlier studies with less intense and prolonged therapy (CCG-551, -503, and -552) had a 2-yr EFS of 55±2.5% while CCG-5911 short but intensive therapy pts had a 2-yr EFS of 80 ± 6% ($p<0.01$). Overall, pts ≥15 yrs at diagnosis had an inferior outcome to younger pts (5-yr EFS: ≥15 yr, 31 ± 7% vs. <15 yr, 57 ± 4%, $p<0.01$). Bone marrow involvement portended a worse prognosis, but outcome for this group of pts was superior on CCG-5911 (73±11% vs. 37 ± 5% on D-COMP [CCG-503] and 48 ± 11% on CCG-552, $p<0.05$). CNS disease did not appear to influence outcome. LDH <500 was associated with a significantly superior outcome (4-yr EFS: LDH <500, 71 ± 4% vs. ≥500, 48 ± 3%, $p<0.0001$). Good risk pts (BM^-, CNS^-, LDH <500) had a significantly improved 4-yr EFS (72± 4% vs. 48 ± 3%, $p<0.0001$). Newer approaches utilizing short but intense therapy offers improved survival for children with disseminated SNCL.

O-152

THE CURRENT ROLE OF SURGERY IN ABDOMINAL NON-HODGKIN'S LYMPHOMAS

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Introduction: The role of surgery in abdominal non-Hodgkin's lymphoma (NHL) in children has changed in the last few years. The aim of this study was to review our surgical approach since 1983. ***Material and Methods:*** The clinical histories of 88 children diagnosed of NHL; 32 thorax and neck excluded from the study, and 56 abdomen (39 boys, 17 girls; age range: 2-15 years; mean age: 9 years) at our centre between 1983 and 1996 were studied. Tumours were 10 stage II, 29 stage III and 17 stage IV. Laparotomy was performed in 22 patients (39%): 12 (8 stage II, 3 stage III and 1 stage IV) with complete abdominal mass resection (9 with intestinal intussuspection, 1 acute appendix, 1 bowel wall infiltration and 1 retrovesical tumour with mesenteric lymph nodes) and 10 with abdominal tumour biopsy (7 stage III, 3 stage IV). In the remaining 34 patients diagnosis was established by pleural and/or ascitic cytology and/or lymph node and/or bone marrow biopsy. ***Results***: Of the surgical group, two patients presented post-operative complications, 1 intestinal perforation and 1 intestinal occlusion because of which chemotherapy was delayed. Of these 56 patients, 4 stage III (7%), and 5 stage IV (9%) died; 2 patients are under treatment and 1 with HIV and stage IV abandoned treatment. The remaining 44 patients (78%) are alive and in complete remission. ***Conclusions:*** 1.- Major surgery in advanced stages is contraindicated since it implies high morbidity, delays chemotherapy and fails to improve survival. 2.- Total tumour resection is only justified in localized stage II disease since it reduces chemotherapy courses and does not imply high morbidity.

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ICE THERAPY FOR RECURRENT NON-HODGKIN'S LYMPHOMA OF CHILDHOOD

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As single agents, Ifosfamide, Carboplatin and Etoposide all showed activity in the treatment of recurrent non-Hodgkin's lymphoma (NHL). In POG protocol #8763, the combination of Ifosfamide and Etoposide (IE) produced 1 CR and 1 PR in 17 patients with recurrent NHL, a CR+PR rate of 12%. In a follow-up study, POG investigated the usefulness of a 3 drug combination with IE + escalating doses of Carboplatin (ICE) in treating children with recurrent NHL.
Patients and Methods: The ICE regimen is composed of Ifosfamide 1.5 gm/m^2, Etoposide 100 mg/m^2, both given ivqd x 3, and Carboplatin 635-700 mg/m^2 iv on day 3 only. Twenty-two previously heavily treated patients with age ranging from 2-20 years (median 12 years) were registered on study. Eighteen of the 22 patients had advanced stage 3-4 disease.
Results: Twenty evaluable patients tolerated up to 6 courses of therapy (range 1-6, median 2). The response rate (CR + PR) increased dramatically to 70% (14/20 patients). Responses occurred rapidly after only 1 to 2 courses of ICE therapy. Twelve of the 14 responders went on to bone marrow transplantation. Myelosuppression was the dose limiting toxicity with ANC <500/μl in 80% of the patients, and platelet count <25,000/μl, in 35%. Even though no cytokines were used to ameliorate the severe neutropenia, only 2 patients needed dose reduction and all patients received their therapy within 4 weeks. Microscopic hematuria was seen in 2 patients. No Fanconi's syndrome was reported.
Conclusion: ICE is an effective combination as salvaging therapy for recurrent NHL of childhood.

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INTRAVENTRICULAR (IVT) CONCENTRATION x TIME METHOTREXATE (MTX) AND CYTOSINE ARABINOSIDE (Ara-C) FOR MULTIPLE MENINGEAL RECURRENCE OF CHILDHOOD LEUKEMIA/LYMPHOMA: A 30% LONG TERM SURVIVAL.

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Intrathecal (IT) or high dose IV chemotherapy regimens for meningeal relapse in children with leukemia/lymphoma who have previously received preventive or therapeutic cranial radiation (CR) can induce remission, but few patients (pts) are cured. IVT administration of chemotherapy via a subcutaneous reservoir attached to a catheter in the lateral ventricle allows for more uniform drug distribution in the subarachnoid space and more flexible drug administration schedules. We report our experience over the past 10 years with 21 pts, with a median of 3 meningeal relapses (range: 1-11) treated for a cumulative of 488 months for multiple recurrent meningeal disease. The induction regimen consists of 2 mg MTX daily for 3 days (CxT) via an Ommaya reservoir (OR), repeated every 10 days for 4 courses. Once in remission, pts received alternating IVT CxT Ara-C (15 mg/day) or MTX (2 mg/day) daily, for three days every 2 weeks for 4 courses and then monthly. Pts median age was 5 yrs at diagnosis, 8 yrs at first CNS relapse and 12 yrs when starting CxT. 18 pts had ALL, 2 had Burkitt's lymphoma and 1 had undifferentiated leukemia. These heavily pretreated pts had received standard IT MTX and Ara-C, a median of 2400 cGy (range: 1800-4900 cGy) of CR and 0-5 experimental treatment modalities (e.g., IT diaziquone, IT mercaptopurine, and IT Mafosfamide). 20 of the 21 pts achieved a complete remission (absence of leukemic blasts in CSF cytospin) in a median of 10 days (range: 2-40 days). Median remission duration to next CNS relapse was 21 mo. (range: 2-81 mo.). 14 pts have died of recurrent disease or treatment complications (e.g. BMT), 1 was lost to follow-up, 3 are continuing treatment at 25, 66 and 81 months and 3 are alive and off treatment for 1, 4 and 7 yrs. (the latter pt relapsed on CxT and then received CR. Toxicities reported more often with Ara-C, were chemical arachnoiditis (4 episodes) and intermittent headaches (6 pts) that frequently responded to concurrent administration of Hydrocortisone. Infection and malfunction of the OR occurred infrequently. This IVT CxT regimen appears to be a relatively effective and well tolerated treatment for recurrent meningeal leukemia/lymphoma.

O-155

RESULTS OF A RANDOMISED TRIAL ON PROPHYLACTIC G-CSF DURING INDUCTION TREATMENT OF NON-HODGKIN'S LYMPHOMA.

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The GL93 study was run by the SFOP to assess the potential benefit of prophylactic G-CSF in the 2 consecutive induction courses called COPAD(M) (cyclophosphamide 0,5 or 1 g/m^2 d2-4, vincristine 2 mg/m^2 d1 $\pm$ d6, prednisone 60 mg/m^2 d1-7, adriamycine 60 mg/m^2 d2, $\pm$ high dose methotrexate 3 or 8 g/m^2 d1) of the LMB 89, LMT 89 and HM91 protocols for respectively B-cell, T-cell and anaplastic large cell lymphomas. Patients (Pts) were randomised to receive (GL+ arm), or not (GL- arm) G-CSF (lenograstim) 5 µg/kg/j started d7 and stopped when neutrophils (PN) were $\geq$

0.5 x 10 ^{9}/l during 48 h. Pts with known infection were not included. From january 1994 to june 1996, 149 pts were registered from 28 french centers, 148 are evaluable. Distribution was similar between the 2 arms in terms of sex, age, primary site, stage and protocols. Results (% or median and range) are summarised in the following table :

	1st COPADM			2nd COPADM		
	GL+	GL-	P	GL+	GL-	P
Patients	75	73		75	72	
Incidence (%)of febrile neutropenia	89 %	93 %	NS	88 %	88 %	NS
major infection	9 %	14 %	NS	14 %	10 %	NS
Duration (days) of neutropenia	3 (0-18)	6 (0-17)	10^{-4}	4 (0-19)	7 (0-22)	10^{-4}
hospitalization	15 (4-28)	16 (5-35)	NS	15 (3-30)	16 (4-69)	NS
IV antibiotics	6 (0-23)	7 (0-29)	NS	7 (0-36)	8 (0-31)	5 %
Intervals between courses (days)	19 (14-31)	20 (14-42)	10^{-1}	21 (17-50)	22 (16-40)	NS

In total : duration of neutropenia (PN < 500) was shorter in GL+ arm, but % of febrile neutropenia and major infection, durations of hospitalisation and IV antibiotics, % of red cell or platelet transfusions and of grade 3-4 mucositis were not different. Relapse rate and EFS at 2 years were similar in both arms. In conclusion : prophylactic use of G-CSF (5 µg/kg/d) after COPAD (M) courses has no clinical impact and is not recommended for systematic use.

(work supported by PHRC and Bellon).

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THE *AF10* GENE FAMILY IS DEFINED BY A LAP DOMAIN AND AN ADJACENT HV BOX, FEATURES ALSO FOUND IN *MLL*

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Introduction: We have previously identified the t(10;11)(p12;q23) breakpoint in acute myeloid leukaemia (AML). This translocation fuses the *MLL* gene on 11q23 with *AF10* on 10p12. Both genes contain cysteine rich regions (CRR) with characteristics of zinc fingers, MLL towards its centre and AF10 at the N-terminal end. AF10 also has a leucine zipper (LZ) towards the C-terminus. Methods and Results: RT-PCR analysis of 10 patients with AML and the t(10;11) translocation revealed a heterogeneity of breakpoints on AF10 with clustering seen in childhood leukemias. Though this suggests different mechanisms for translocation in children and adults, the end result was always the loss of the CRR of both MLL and AF10 in the critical der(11) product. The properties of the CRR region of AF10 were examined by cloning into an expression vector. Spectrophotometric analysis of the recombinant protein suggested metal-ion binding properties. The protein failed to bind DNA in band shift assays but was seen to bind other protein(s) on western blotting. Computerised homology searches of the AF10 CRR identified 31 other proteins including MLL with a similar CRR. Since this highly conserved region has the features of a novel zinc finger and at least 6 members are involved in leukaemia associated translocations we have named it the leukaemia associated protein or LAP finger. Close homology in the LAP domain and LZ regions of AF10 is observed with the HRX partner gene AF17, the human gene BR140 and the *C.elegans* gene Cezf. Just downstream of the LAP fingers of these proteins is another CRR with histidine and valine residues. We have named this the HV box. Low stringency southern analysis using this region as a probe suggested the presence of additional genes with similar characteristics. Degenerate PCR primers were used to identify at least two other human genes with a LAP finger and HV box characteristic of the AF10 gene family. Conclusions: The AF10 gene family is characterised by a single LAP finger followed by an HV box. This motifs are likely to be protein interactive domains and are consistently lost in the t(10;11) and t(11;17) translocations seen in AML.

O-157

DO THE P16^{INK4} AND P15^{INK4B} PROTEINS MEDIATE SENESCENCE IN T-CELLS?

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Objective: In ALL inactivation of the p16^{INK4}-tumour suppressor gene may be the most common genetic alteration and has a predilection for T-cell disease. The role of the neighbouring p15^{INK4B}gene in tumour suppression is not conclusively defined. The aim of the present study was to elucidate the role of regulators of the cell cycle in T-cells, particularly the p16^{INK4}/p15^{INK4B} proteins.
Materials and Methods: Normal T-cells were obtained from healthy blood donors. Proliferation was induced by PHA and IL-2. After nine days of culture, the cells were either challenged by withdrawal of serum or IL-2 or maintained in culture until senescence. The levels of cell-cycle regulating proteins and complexes were monitored by western blotting and immunoprecipitations and the activity of CDK2 and -6-complexes was measured by kinase assays .
Summary of Results: The dominating CDK-inhibitor in quiescent T-cells is p27^{Kip1}, which is down-regulated during proliferation. The p16^{INK4} protein is undetectable in resting T-cells, but is induced promptly when the cells begin to proliferate. P15^{INK4B} is expressed at low levels in resting cells and is also induced during proliferation. The levels of both proteins accumulate during proliferation until senescence. Challenge by serum or IL-2 deprivation results in growth-arrest, accompanied by reinduction of p27^{Kip1}, and in serum starved cells, induction of p21^{Cip1}. P16^{INK4}-levels drop sharply in cells deprived of IL-2. In cells allowed to continue into spontaneous senescence, the levels of both the p16^{INK4}/p15^{INK4B} proteins and p27^{Kip1} increase. The kinase activity of CyclinD-CDK6-complexes seems to be inhibited by binding of p16^{INK4} protein in senescent cells.
Conclusion: The p16^{INK4}/p15^{INK4B} proteins may control the growth of expanding T-cells, setting a "threshold" beyond which clones cannot expand. These proteins may thus be involved in T-cell senescence. The expression of p16^{INK4} is directly or indirectly dependent on IL-2. The findings are consistent with a role for the p16^{INK4}/p15^{INK4B} proteins as tumour suppressors in ALL.

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EPSTEIN-BARR VIRUS INFECTION STATUS IN HODGKIN'S DISEASE-DERIVED CELL LINE L591

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The frequency of Epstein-Barr virus (EBV) presence in Hodgkin's Disease (HD) is similar to that found in nasopharyngeal carcinoma and raises questions about a possible involvement of the virus in the pathogenesis of HD. In order to characterise EBV infection and to discriminate its intracellular DNA forms (linear, episomal, integrated), we analysed the EBV-positive Hodgkin's disease-derived cell line L591 employing morphological criteria for distinguishing different EBV patterns. Fluorescence *in situ* hybridisation (FISH) with the BamHI W fragment of the viral genome in combination with immunocytochemical analysis of virus-encoded proteins (EBNA2, LMP, ZEBRA) or the human Ki-1 antigen was performed on interphase nuclei. Virtually all L591 cells were Ki-1 positive and contained both the latent and to a minor extend the lytic virus. The latent infectious state of EBV was confirmed by the high level of LMP expression. Although EBNA2 is not expressed in HD tissues, about 40% of the L591 cells were positive. FISH analysis revealed a signal type representing integrated and episomal viral populations within the same nuclei in the majority of the latently infected cells. The question whether the L591 cell line may harbour integrated viral copies was assessed by the demonstration of non-random distribution of EBV-FISH signals on metaphase chromosomes. The most frequently involved chromosomal bands were 1p35-36, 1q43, 4q23, 4q32, 6q24, and 13q13. The lytic activity was high and about 25% of cells displayed FISH signal types representing virus in budding or

release. These signal types correlated with ZEBRA expression. Interestingly, LMP and ZEBRA were coexpressed in about 10% of the cells in the lytic cycle. Thus, in the cell line L591 both latent and lytic forms of EBV can be observed and reliably discriminated by FISH and immunocytochemistry. Moreover, integration of the virus in the host genome at specific loci is a constant feature in the cell line L591 resembling the integration pattern found in lymphoblastoid cell lines.

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THE HUMAN POLYOMAVIRUS BK IS PRESENT AND ITS LARGE TUMOR ANTIGEN IS EXPRESSED IN NEUROBLASTOMAS

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These studies were initiated in order to examine whether genomic sequences from potentially oncogenic human polyomaviruses were present, and oncogenic viral gene products were expressed in neuroblastomas. The background and rationale for this was that such tumors are induced in transgenic mice expressing the large T(tumor)-antigen of human polyomaviruses, and that BKV DNA sequences have been detected in human neuroblastoma cell lines as well as in neuroblastoma tissue from one patient.

BKV infects children all over the world, seemingly without giving any serious symptoms. Following primary infection the viruses establish latent or persistent infections, and may become reactivated by immunosuppression.

Based on this background and given the opportunity to employ new and more sensitive, including *in situ*, techniques, we initiated a search for BKV DNA as well as large T-antigen in human neuroblastomas.

Materials and Methods. 19 samples from neuroblastomas and 5 samples from normal adrenal glands were examined for BKV using the following methods: PCR on tissue extracts, PCR in situ, in situ DNA hybridization, immunoperoxidase for detecting T-ag.

Results: The presence of BKV DNA was found in all 19 neuroblastomas and 1 of 5 normal adrenal glands by PCR on tissue extracts. Using DNA in situ hybridization and PCR in situ the same results were found. Expression of large T-antigen was detected in 17 of 19 neuroblastomas.

Discussion and Conclusion: It is potentially significant and important to find an oncogenic virus present and a viral oncogenic gene product expressed within the transformed cells in such a high number of neuroblastomas

The presence of BKV sequences in neuroblastomas does not by itself establish a cause-and-effect relation to the initiation or development of the tumor. Most people have been infected by BK virus by 10 years of age and viral DNA sequences could simply be an incidental finding in tissues of persons previously infected. However, different lines of evidence support a possible causal relation between these viral sequences and tumor formation. The molecular mechanism that needs to be evaluated is a possible inactivation of p53 by polyomaviral T-antigen. This could block the antiproliferative function of p53, thereby promoting tumorigenesis.

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EVALUATION OF THE IL-2 INDEPENDENT ACTIVATED NATURAL KILLER CELL LINE, NK-92, AS A POTENTIAL THERAPY FOR NEUROBLASTOMA.

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The NK-92 cell line displays characteristics of lymphokine-activated killer (LAK) cells although it has much more lytic ability with a broader spectrum of targets. Also, NK-92 does not express the inhibitory p58 receptor normally seen on LAK cells. NK-92 was initially IL-2 dependent until it was transfected with an cPep-based transfectant expressing IL-2 (NK-92ci). We hypothesized that the NK-92 cell line may be a potential therapy for neuroblastoma. The lytic ability of the transfected IL-2 independent cell line, NK-92ci, was compared to the parent IL-2 dependent cell line and LAK cells against neuroblastoma and control cell lines using a 4-hour chromium release assay. Evaluations were made on the ability of NK-92 to kill neuroblastoma cells by induction of apoptotic (DNA fragmentation) or by perforin mediated pathways using agents known to block perforin exocytosis. We immunophenotypically evaluated whether target cell lysis was dependent on expression of ICAM-1 as is seen with LAK-mediated lysis. Lysis by the transfected NK-92ci cell line and the IL-2 dependent NK-92 are identical, but better than LAK cells. NK-92ci had significant lytic activity against an ICAM-1 positive neuroblastoma cell line (SKNAS), with less against ICAM-1 weakly positive (IMR-32 and SAN-2), and no activity against ICAM-1 negative lines (KCNR and N6F). NK-92 did not induce apoptosis in the K562 (CML, + control), SAN-2 (neuroblastoma) and SR-91 (lymphoma, - control) cells lines during a 4 hour incubation. Lysis by NK-92 was inhibited by drugs (EGTA and cyclosporin A) that interfere with exocytosis and perforin polymerization. NK-92ci was able to induce significant cell killing in ICAM-1 expressing neuroblastoma cells without exogenous IL-2. Exocytosis of perforin appears to play a role in target cells lysis by NK-92. NK-92ci may be effective for *ex vivo* purging of neuroblastoma from marrow or blood stem cells or as *in vivo* therapy. NK-92 is currently being evaluated in phase I clinical studies.

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GDNF-INDUCED DIFFERENTIATION AND EXPRESSION OF RET TYROSINE KINASE AND GDNFR-α IN HUMAN NEUROBLASTOMAS

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Neuroblastoma is originated from the neural crest and often undergoes spontaneous differentiation and regression. Recent studies have revealed that neurotrophic factors and their receptors may play an important role in regulating the differentiation and the cell death of the tumor. Glial cell line-derived neurotrophic factor (GDNF) promotes survival of the dopaminergic neurons in the central nervous system as well as the neurons of the peripheral nervous system. Here we studied the effect of GDNF on thirty-eight human neuroblastomas in primary culture, and examined mRNA expression of both a Ret tyrosine kinase receptor gene and a GDNFR-α GPI-linker receptor gene in the tumors. The human GDNFR-α was cloned by screening a human adult substantia nigra cDNA library. Thirty-two out of 38 primary neuroblastomas responded to GDNF by extending neurites independent of disease stages. However, the treatment of the cells with both GDNF and retinoic acid dramatically enhanced neurites extension, which was seen more often in the favorable tumors than in the stage 4 tumors. The RT-PCR analysis showed that both Ret and GDNFR-α were frequently expressed in the tumors. Nevertheless, in some tumors, there found a dissociation between the responsiveness to GDNF and the expression of Ret and/or GDNFR-a. These suggest that many human neuroblastomas express Ret and GDNFR-α, and respond to GDNF to differentiate. The GDNF signalling in neuroblastoma may have an important role in regulating the clinical biological behavior of the tumor.

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p53 AND RELATED PROTEIN EXPRESSION BY IMMUNOHISTOCHEMISTRY IN NEUROBLASTOMA

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Background: Despite the lack of p53 mutations in neuroblastoma, wild type p53 has been reported to be overexpressed and abnormally located in the cytoplasm of neuroblastoma where it may be non-functional and unable to upregulate genes such as *WAF-1*. Aims: The present study further investigates p53 and related protein expression in neuroblastoma. Methods: 13 formalin fixed, paraffin embedded sections were obtained from 12 neuroblastoma patients before chemotherapy, 1 stage 3 with *MYCN* amplification (*MYCN*A), 10 stage 4 (2 *MYCN*A), 1 stage 4s and 1 from a patient with a ganglioneuroma. Wild type and mutant p53 was detected and localised by immunohistochemistry using D0-7 and DO-1 monoclonal antibodies. In addition, Ki-67, BCL-2 and WAF-1 expression were also studied. Slides were scored positive for p53 if >10% of cells were immunostained. Results: Nuclear p53 expression was present in 5/13 patients using D0-7 and 4/11 using D0-1 antibodies. p53 positivity was related to adverse clinical outcome using Log Rank analysis p=0.009 (DO-7), p=0.05 (DO-1), but was not related to age (< or > 1 year), stage or *MYCN*A. In this small sample there was no relationship between BCL-2, Ki-67 or WAF-1 expression and age, stage, *MYCNA* or survival. However, 3 patients with <10% p53 positivity, all of whom all survived, had >5% WAF-1 expression (2 stage 4 and 1 stage 4s). Conclusion: Nuclear p53 expression is present in neuroblastoma and may be a poor prognostic indicator. Confirmation of these results by a larger study is in progress.

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SOMATOSTATIN INHIBITS NEUROBLASTOMA GROWTH *IN VIVO*.

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Introduction: We recently reported that the neuropeptide somatostatin is highly expressed in benign ganglioneuromas and in differentiated neuroblastomas. Somatostatin expression is associated with favourable prognosis in children over one year of age with advanced neuroblastoma (INSS 3 and 4). In addition, high-affinity somatostatin receptors (SR) are preferentially expressed in neuroblastomas of localised stage with favourable biological features. Together, these findings suggest that somatostatin may play a functional role in human neuroblastoma regression *in vivo*. Since somatostatin analogues may induce apoptosis and inhibit neuroblastoma cell growth *in vitro*, we investigated the effects of the somatostatin analogue octreotide on neuroblastoma growth *in vivo*.
Methods: Nude rats with human neuroblastoma SH-Y-5Y xenografts were treated 14 days with octreotide (10μg s.c. every 12h). The rats were examined for *in vivo* expression of SR with 111-In-pentetreotide. Serum IGF-I was measured as an intermediate marker for somatostatin activity.
Results: Somatostatin receptor expression *in vivo* was upregulated in rats treated with somatostatin compared to the untreated control group. Moreover, somatostatin therapy reduced the growth of xenograft tumours (n=7, median weight 3.03 g) compared to untreated control tumours (n=8, 7.44 g, p<0.012). Serum IGF-I decreased during somatostatin therapy.
Conclusions: Somatostatin may have an autocrine upregulating effect on specific receptors *in vivo*. Treatment with somatostatin may significantly decrease neuroblastoma tumour growth *in vivo*. Further studies are warranted to establish the role of somatostatin analogues in the treatment of children with neuroblastoma.

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Gain of chromosome arm 17q: a poor prognosis indicator in neuroblastoma

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Comparative genomic hybridization studies have revealed gain of the long arm of chromosome 17 to be the most frequent genetic abnormality in neuroblastoma cells. Using fluorescent in situ hybridization of tumour metaphases, we have shown that the form of this gain is almost invariably unbalanced translocation resulting in partial trisomy for 17q12-21 to 17qter. Review of the literature indicates that these translocations can involve at least 25 different sites on 15 partner chromosomes. This unusual promiscuity of translocation partners suggests that 17q12-21 may be the site of an important gene in neuroblastoma biology.
To investigate the clinical importance of 17q changes, we determined the 17q status of 45 primary neuroblastoma tumours by cytogenetics, FISH and CGH. Gain of 17q was found in 28 tumours and was associated with known clinical and genetic indicators of poor prognosis; age>1 year, stage 4 disease, 1p deletion, MYCN gene amplification and diploid/tetraploid chromosome number. Survival analysis showed that partial gain of 17q is significantly associated with poor overall survival - 8% at 4 years compared with 100% for cases without 17q gain ($p = 0.0001$). 17q status also has a significant effect within the MYCN non-amplified group.
We conclude that gain of 17q is the most common abnormality in neuroblastoma cells, and is a powerful independent indicator of poor prognosis. It seems likely that this genetic aberration plays a fundamental role in progression of this tumour.

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ALLELOTYPING OF RHABDOMYOSARCOMA

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Objective Rhabdomyosarcoma (RMS) histologically classified as embryonal (e) or alveolar (a) account for approximately 10% of solid childhood tumors. Precise diagnosis is required since aRMS have a significantly poorer prognosis. However, undifferentiated RMS and mixed types with partly alveolar differentiation pose difficulties in terms of defining the exact diagnosis. Cytogenetically and molecular genetically, aRMS are defined by reciprocal t(2:13) or t(1:13), whereas eRMS have demonstrated frequent LOH at chromosome 11p15.5.
Methods CGH was performed on 18 cases, of which 9 were of alveolar type with proven t(2;13) or t(1;13) translocations. PCR-based microsatellite analysis of 11p15.5 and 11q23 chromosome regions was done on all cases. Ploidy status of chromosome 11 was examined by FISH technique.
Results CGH of eRMS revealed low level gains of genetic material mostly involving the entire length of chromosome 2, 8, and 11. In almost all aRMs genomic amplifications with multiple amplicons were detected. Amplicons were localized to 1p36 (1/9) and 2q35 (3/9) and spanning to the MYCN locus at 2p23-24 (3/9). LOH of loci on chromosome 11 was found in 4/9 aRMS and 8/9 eRMS. Whereas in only one case LOH results were consistent with CGH, FISH-analysis demonstrated two or more copies of chromosome 11 in the other cases with LOH.
Conclusions These data suggest that eRMS and aRMS are genotypically distinct tumor types with a characteristic low level gains in eRMS and regional high level amplifications in aRMS. Gains of chromosome 11 demonstrated by CGHand FISH with simultanous LOH of 11p15.5 and 11q23 in microsatellite analysis suggest loss of constitutive heterozygosity selectively involving a specific parental chromosome resulting in uniparental di- or polysomy.

O-166

LOH OF CHROMOSOME 17P IN PNET: MOLECULAR ANALYSIS AND CLINICAL SIGNIFICANCE.

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Isochromosome 17q is associated with loss of heterozygosity of chromosome 17p (LOH 17p) and is the most common genetic aberration in childhood medulloblastoma and primitive neuroectodermal tumors (PNET). To determine frequency, extent and clinical significance of 17p deletions, 29 loci on 17p were investigated in 24 tumors using microsatellite analysis resulting in an average spacing of markers of less than 1 Mb. LOH 17p was found in 11 out of 26 tumors. In all tumors with LOH a continuous stretch from the telomer to band 17p11.2 was completely deleted, no interstitial or terminal small scale deletions were detected in the remaining 15 tumors. In 4 tumors with LOH 17p the chromosomal breakpoint was located between D17S953 and D17S805. Our data were verified by fluorescence in situ hybridization (FISH) analyses using two YAC clones, positive for D17S689 and D17S953, respectively. Therefore in most childhood PNETs with LOH of 17p, the breakpoint is close but not within the centromer. It varies and predominantly occurs between the two markers D17S689 and D17S953, an unstable chromosomal region that is deleted or duplicated in the Smith-Magenis syndrome (SMS). To determine the clinical significance of this aberration the patients´ clinical data were analyzed. Among 32 tumors and metastasis investigated 16 showed LOH 17p. 11 patients displayed primary metastasis at time of presentation.The outcome of patients with LOH 17p in the tumors was significantly worse compared to controls.
Our study provides entrypoints to determine the molecular nature of LOH 17p in PNET and to analyze mechanisms of formation of an i17q, the most common isochromosome in human cancer. Moreover these data suggest that LOH 17p is a prognostic parameter predicting aggressive disease and poor outcome.

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CHILDHOOD NON HODGKINS LYMPHOMA - DISEASE PROFILE AND SURVIVAL

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Children with non Hodgkins Lymphoma (NHL) were retrospectively reviewed with respect to site of primary disease, histologic subtype, staging, treatment and outcome following the implementation of specific chemotherapy regimens based on histology and stage.
Data was available on 104 patients (54 Black, 44 White, 3 Asian, 3 Mixed parentage) from 1983 to 1996. Male to female ratio was 2,7:1. Median age at diagnosis was 6,53 years (range 7 months to 16,5 years). The site of primary disease was abdominal in 22% of Black children, 59% of White children; mediastinal in 40% of Black children, 32% of White children, other sites including bone and jaw were seen in 37% of Black children and 9% of White children. Histologic diagnosis according to the Working Formulation confirmed all cases to be high grade lymphomas, 38% lymphoblastic, 40% Burkitts, 11,5% Large cell, 5% Ki-1 large cell anaplastic. The distribution of histologic subtypes was not significantly different between Black and White children. The clinical staging according to Murphy's staging system was Stage I - 3 (2%), Stage II - 24 (23%), Stage III - 47 (45%), Stage IV - 23 (22%). There was a higher incidence of Stage IV disease in Black children 29% vs 18% in White children. The overall survival for Black children was 46,3% and for White children 79,5%. The difference in survival reflects the higher incidence of Stage IV disease, early complications of therapy and poor nutritional status in the Black children.

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LEUKAEMIA AND LYMPHOMA IN ASIAN CHILDREN LIVING IN THE WEST MIDLANDS REGION, UK, 1978-92

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Objective - This was to determine the patterns of leukaemia and lymphoma in White and Asian children living in the West Midlands Region of the UK (population 5.2 million, including 1 million children of whom in 1991 10% were of Asian origin).

Methods - Data were obtained from WMRCTRG and age standardised incidence rates (ASR) and sex ratios were calculated. Age at diagnosis and the distribution of ALL, AML and lymphoma subtypes were recorded.

Results - Between 1978 and 1992, 536 white and 58 Asian children were registered with leukaemia. ASR's for ALL were identical in the two ethnic groups at 34.7 per million per year. AML rates were similar at 6.8 and 6.3 respectively. The sex ratio was similar (1.48 for Whites, 1.42 for Asians), as was distribution of ALL and AML subtypes, and age at diagnosis.

In the same years 135 White and 32 Asian children were registered with lymphoma. The ASR for lymphoma was 22.3 in Asian and 9.1 in White children ($p<0.01$) being doubled for both Hodgkin's and non-Hodgkin's lymphoma in Asians compared with Whites. The sex ratio was higher in Asian than White children (5.4 compared to 2.6, p 0.18). Age at diagnosis was significantly lower in Asians (median 10 years 5 months for Whites, 7 years 2 months for Asians, p 0.03). In 22% of Asian children congenital abnormalities were present.

Conclusions - Asian immigrants to the UK show the same incidence and pattern of childhood leukaemia as Whites. However in Asians the incidence of lymphomas is double that in Whites, M:F sex ratio is higher and age at diagnosis is lower. While infections have been implicated in the aetiology of both leukaemias and lymphomas, the striking differences in the patterns of these diseases in Asians compared with Whites suggest that their aetiology may differ. In lymphomas ethnically determined genetic predisposition may be important.

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SEASONAL VARIATIONS IN ONSET OF HODGKIN'S DISEASE(HD)AND ACUTE LYMPHOBLASTIC LEUKAEMIA(ALL)IN NORTH WEST ENGLAND.

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Analyses of Manchester Children's Tumour Registry (MCTR)data have shown increases in incidence of ALL and HD but not of AML and NHL.Evidence of space-time clustering was found in ALL and HD but not AML and NHL.These findings suggested the influence of environmental factors,possibly infections,in the aetiology of ALL and HD.We have now examined seasonal variations in onset of leukaemias and lymphomas included in the MCTR,1954-1996.Cases were analysed by season of diagnosis and separately for season of first symptom.The latter was defined as the date on which the child was last thought to be well and has been prospectively recorded by the MCTR since 1954.Seasons were defined as Spring(M,A,M)Summer(J,J,A)Autumn(S,O,N)and Winter(D,J,F).Observed cases in each season were compared

with expected assuming a uniform distribution.Similar analyses by month of diagnosis and month of first symptom were also performed.No significant deviations from expected numbers were observed for dates of diagnosis.However,there was significant evidence of departures from a uniform distribution with respect to dates of first symptom for ALL with peaks in April,May and December(p=0.04)and HD with pronounced peaks in Winter(p=0.0001)and December,January and February(p=0.0008).Separate analysis of c-ALL(1979-96 only)showed a peak spanning October,November and December (p=0.056).We conclude that the observed seasonal variation in onset of ALL,particularly c-ALL,and HD taken together with previous results on incidence trends and space-time clustering,support an aetiological role of infections, although different mechanisms may be operating.A candidate organism in HD would be EBV.Date of first symptom more closely approximates disease onset than date of diagnosis.

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THE RISK OF CHILDHOOD COMMON ALL IS ASSOCIATED WITH A SPECIFIC HLA-DQA1-DQB1 HAPLOTYPE

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There are suggestions that childhood common ALL may arise by two-steps in which the second step is promoted by an immune response to a post-natal infection. To determine whether the risk of c-ALL is influenced by genetic factors controlling immune responses, we have carried out a high resolution molecular typing analysis of alleles at the HLA-DQA1 and DQB1 loci in a series of 60 children with c-ALL (38 males, 22 females) in comparison with 78 newborn infants (38 males, 40 females). The results of allele frequency analysis showed an increase of DQA1*0101 in c-ALL compared with controls (Odds Ratio (OR) = 1.96; p = 0.054) which was attributable to an increased risk in males with c-ALL (male c-ALL vs males controls: OR = 2.55, p = 0.049). Classification of patients according to DQA1 and DQB1 type showed that DQA1*0101 and DQB1*0501 almost always occurred together in the same individual, indicating that these two alleles are in linkage disequilibrium. Males with this haplotype showed a strongly increased risk compared with male controls (OR = 9.48; p < 0.001), whereas females with c-ALL did not. These results are supported by segregation analysis of this DQA1-DQB1 haplotype in the families of 24 children with c-ALL. Further analysis suggested that susceptibility may be associated with sequences coding Serine at position 52 of DQA1*0101 and Valine at position 57 of DQB1*0501. One interpretation of these results is that DQA1*0101-DQB1*0501 exerts a greater influence on the risk of c-ALL males than than it does in females.

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INCREASE IN HEPATOBLASTOMA WITH VERY LOW BIRTH WEIGHT IN JAPAN

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To confirm the impression that hepatoblastoma with very low birth weight (HB/VLBW) was increasing, we have accessed the data in the Japan Children's Cancer Registry and have analyzed patients' diagnoses and birth weights. During the 9 years from 1985 to 1993, 38 (0.38%) patients with tumors who weighed less than 1500 gm at birth were identified among 9923 registered patients. Hepatoblastoma was diagnosed in 9 patients of very low birth weight, representing 3.9% of the 231 patients with hepatoblastoma registered. A significant linear trend toward an increase in the percentage of patients with a birth weight of less than 1500 gm was observed specifically in hepatoblastoma (p=0.0047). The percentage rose from 0.7% (1/138) in the 5-year period of 1985 to 1989 to 8.6% (8/93) in the next 4-year period (1990-1993). This increase was attributed to the significant increase in the percentage of patients who weighed less than 1000 gm at birth (p=0.0028). A separate peak in the number of patients in the birth weight range of less than 1000 gm suggests that the cause of HB/VLBW may be different from that of other patients. So far 15 HB/VLBW patients, 9 boys and 6 girls, have been identified. The patients were diagnosed at the age of from 6 to 77 months (median, 16 months). Their birth weight ranged from 560 to 1380 g (median, 826 g) and the gestational age was 23-33 weeks (median, 25 weeks). No congenital malformation or family history suggesting genetic predisposition to the tumor was observed. Full analysis of the patients' data is under way.

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RISK OF CARCINOMA AFTER CHILDHOOD CANCER

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Objectives To investigate the incidence and causes of second primary carcinoma after childhood cancer in Britain.

Methods A cohort of 13279 patients who survived at least three years after of diagnosis of childhood cancer between 1940 and 1983 was established using the population-based National Registry of Childhood Tumour. Occurrences of second carcinoma were identified. A case-control study was also established. Cases were patients developing a second carcinoma, and we attempted to select 4 controls matched to each case. Cumulative doses of radiation and chemotherapy were calculated for the period between the two cancers in each case and for a corresponding interval after the original childhood cancer in the matched controls.

Results A total of 69 second carcinomas were observed within the cohort study, 25 of skin and 44 of other sites. By 30 years from three-year survival 2.5% of patients had developed a carcinoma, 1% of skin, 1.5% of another site. This corresponded to 4, 13 and 3 times the number of such carcinomas expected respectively. There were 12, 9, 9 and 8 carcinomas diagnosed in digestive, breast, thyroid and genito-urinary tissue, respectively. From the case-control study the risk of second carcinoma among patients who received radiotherapy was 2.5 times that experienced by patients who received neither radiotherapy nor chemotherapy (p = 0.026). The risk of second carcinoma increased with increased exposure of tissue to radiation as a result of radiotherapy for the original childhood cancer. Patients who received 2000-2999 cGy and at least 3000 cGy experienced 18 and 12 times the risk associated with tissue that had not been irradiated, respectively (p <0.001 for both comparisons).

Conclusions These data have implications for monitoring patients treated in the past and for planning future treatment protocols to achieve an optimum balance of the risks and benefits of different protocols in the long-term.

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NEUROCOGNITIVE DEFICITS IN MEDULLOBLASTOMA SURVIVORS ARE ASSOCIATED WITH WHITE MATTER LOSS

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Medulloblastoma is the most common malignant brain tumor of childhood. With surgical resection followed by craniospinal radiation therapy (CRT) with or without chemotherapy, long-term survival approaches 60%. However, previous studies have demonstrated a high incidence of neurocognitive deficits among survivors, especially deficits relating to learning and memory processes. These deficits have been attributed to CRT, presumably because of progressive white matter loss secondary to microvascular damage. We studied 45 long-term survivors of medulloblastoma by correlating intellectual (IQ) and academic testing with magnetic resonance imaging (MRI). Patients ranged in age from 2.8 to 16.5 years old at CRT (mean = 8.6, sd = 4.3) and had been treated 2.5 to 10.4 years previously (mean = 4.8, sd = 2.8). Using a Seimens 1.5T Magnetom, a single transverse section from the MRI (T1, T2, proton density) at the level of the basal ganglia, including both the genu and splenium of the corpus callosum, was processed using our automated segmentation algorithm developed from an artificial neural network. As expected, children who were younger at the time of CRT had lower IQs (r = .39). IQ was positively correlated with white matter area uncorrected (r = .49) or corrected for total intracranial area (r = .38). Regression analysis revealed that age at CRT and white matter area accounted for 35.6% of the variance in IQ. Among the academic testing scores, Arithmetic showed the strongest correlation with white matter area uncorrected (r = .46) or corrected for total intracranial area (r = .44). These results support the hypothesis that white matter loss is a mechanism for lowering of IQ among medulloblastoma survivors.

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EVALUATION OF TREATMENT RELATED NEUROPSYCHOLOGICAL DEFICITS IN LONG-TERM SURVIVORS OF CHILDHOOD ALL BY USING FDG PET AND NEUROPSYCHOLOGICAL TESTING

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Prophylactic therapy of CNS with radiation or chemotherapy may be associated with adverse long-term sequelae in acute lymphoblastic leukemia (ALL) patients varying from mild cognitive impairment to serious leukoencephalopathy.
The purpose of the study was to compare effects of CNS radiation plus chemotherapy vs chemotherapy only on cerebral glucose metabolism and neuropsychologic functioning.
We investigated 40 long-term survivors of ALL. All patients were studied with dynamic fluorodeoxyglucose (FDG) positron emission tomography (PET) and local cerebral glucose utilization (LCMRglc) rates were calculated for all brain areas. Patients also underwent intensive neuropsychological testing (attention, memory functions, visual-spatial functions, reading, writing).
Biologically effective radiation dose and cumulative intrathecal and intravenous methotrexate doses were considered as possible risk factors for impairment of neuropsychological functioning. Age and leucocyte count at the time of diagnosis and and age at the time of current studies were taken into account in the analyses.
There were 22 females and 18 males. Mean age at the time of the studies was 16.2 years (8.2-24.8). Mean age at diagnosis was 5.6 years (0.3-15.4). None of the patients had CNS-disease. 20 patients had received both prophylactic radiation and chemotherapy and 20 patients chemotherapy only. These studies were performed at least 36 months after treatment for ALL was finished.
The local or total glucose metabolic rates did not differ between the two treatment groups. It seemed that cerebral metabolism of the brain was not negatively affected in either of the treatment groups. The variability of LCMRglc in our study population may reflect the differences in maturation of CNS at the time of diagnosis and treatment of ALL.

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Altered Body Image Following Adolescent Bone Cancer

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Body image and sexuality are two areas very closely related. For adolescents, the threat of altered body image can be seen as particularly devastating, as sexuality includes both physical and psychological factors, physical appearance as well as sexual activity. Psychological aspects of sexuality include body image which lies at the crux of a person's overall concept of self. When adolescents are facing altered body image, their reactions are similar to those experienced in any loss situation as, in reality, it is a loss as great as death.

Whether the altered body image is transient, as in the case of chemotherapy-induced alopecia, or permanent, as in the case of surgery, it still alters the body's reality from the body ideal. Within the author's unit (orthopaedic oncology), weighing-up what is best for the individual patient is a difficult task. The adolescent faces conflict between preservation of body image, which can be achieved more easily with limb salvage procedures, or the more vigorous function achieved with some amputations. Also, the lack of communication about sexuality can end up as a conspiracy of silence, at just the time when adolescents need to accept their sexuality. The majority of patients want the nurses to address sexuality with them, to explain why the medical treatment may be affecting their biological functioning. It is difficult enough for them to be continually dependant on parents and professionals, due to their illness, without the added feeling that they are not allowed to discuss certain aspects of their care.

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"I AM GOING TO MAKE A LONG JOURNEY": LIFE-SUPPORT OF CHILDREN WHO ARE TERMINALLY ILL

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Background: Nowadays about 70% of children with cancer can be cured. Consequently, there is still a substantial number of children who die of cancer. It is advocated, that children are kept as active and comfortable as possible during their last period of life. They should be bothered at least as possible with hospital visits, and die in the safe and comforting environment of their own home. We report our experiences with a supportive program for the children and their parents to maintain the best quality of life during this period.
Method: In the program a consultant pediatric oncology nurse is essential. When the child enters the terminal phase, the nurse explores the wishes of child and family whether they want to let the child die at home or in the hospital. The nurse discusses with the family in what way the best quality of life can be achieved and how a network in the home environment can be arranged to provide optimal medical and palliative care. The specialized nurse has contacts with the general physician, local pediatrician, and district nurse. All decisions about care are planned in close collaboration with the pediatric oncologist. After the child dies, the nurse has regular contact with the family.
Results: From January 1994 till February 1997, 42 patients were eligible for the program. Two families decided to let their child die in the hospital. Of the remaining 40 families, 39 children (98%) died at home. Only in one family, the mother became physically exhausted and the child was admitted to the hospital shortly before dying. Most children wanted to live their life as normal as possible. They indicated that they knew they were dying and wanted to say "goodbye". It is very important to be aware of subtle signals of the dying child and to translate them into supportive measures. Of the 40 families in the program, 39 families reported positive feelings about having their child die at home.

Conclusion: Almost all children and their parents wished to stay at home in the terminal phase. A program such as here described allows the child to die at home. It is essential that a supportive network is organized, leading to an integrated care by the local and the hospital staff. After the death of the child, it is essential that support to these families is continued.

O-177

The Role of Child Life Intervention in Pediatric Radiation Oncology

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Purpose: A pilot program utilizing a child life specialist in the radiation oncology department was designed in response to the increased use of conformal techniques in radiation therapy. Such techniques require greater precision and longer treatment times. Therefore a preparation program was designed to ensure patient cooperation and decrease the need for daily anesthesia in young patients.
Methods: The preparation program included:
1) Assessment of the needs of each child physically, emotionally and developmentally
2) Introduction of the child to the radiation therapy procedures in a developmentally appropriate manner (familiarizing the child with equipment, staff, environment, sights, sounds and smells)
3) Achieving motion control by instructing the child to inhibit voluntary movements using individualized developmentally appropriate techniques
4) Supervision of the child life playroom/pediatric waiting room in the radiation therapy department

The intention of this design was to promote a high degree of cooperation on the part of the child and the family with a focus on children between the ages of three and six because this age group has traditionally required anesthesia.
Results: Since March of 1996 the BWH radiation oncology department has treated 96 pediatric patients. Of these 96 children, 34 children were between ages of 3 and 6. Eighty-five percent (29 of 34)of the children completed their radiation treatment without the need for anesthesia
Conclusion: A child life program/specialist within a pediatric radiation oncology practice will decrease the need for anesthesia in patients age 3-6 years old. We found that through this intervention we decreased the overall treatment time for the patients and increased the efficiency of the department. The multi-disciplinary team approach and the quality of life benefits to the patients and their families will be discussed.

O-178

LONG TERM EFFECTS OF TREATMENT OF CHILDHOOD LYMPHOMA

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Merrick J, Clinical Nurse Specialist, Late Effects Oncology,
Oncology Unit, The New Children's Hospital, Westmead NSW 2145 Australia.

We have been running a long-term follow-up clinic for survivors of childhood cancer since 1989. Over 500 patients have been followed.

A significant proportion of these patients have survived lymphoma. Patients are eligible for the clinic after they have been disease-free for five or more years off treatment.

We plan to present details of the long-term effects of the various treatment modalities (surgery, radiotherapy, chemotherapy) as well as psycho-social outcomes for this group of patients.

Areas for discussion will include growth, fertility, hormonal and thyroid function.

O-179

BONE MARROW TRANSPLANTATION IN CHILDHOOD SHOULD TAKE PACE IN A PEDIATRIC DEPARTMENT

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In Norway, with a total population of approx. 4 mill, all bone marrow transplants are centralized to the National Hospital in Oslo. All allogeneic and autologous bone marrow transplantations to children age 0 to 15 years are done in the Pediatric Department, in Pediatric Oncology Ward 6, and not at the adult transplant center.

From the pediatric nurses' point of view, we are better qualified to accommodate the child's special needs for care and nursing.
Our goal is to help the child to live a life as normal as possible, and to focus on the child's resources during the time in isolation.
To avoid some of the negative psychosocial effects of strict isolation, we have permitted the patient to move freely in the room. We use single room isolation without laminar air flow.
The parents can stay with their child as much as they like, and we allow private toys and personal belongings. We offer daily primary teacher or school teacher, music therapy and pediatric physiotherapy for all the patients.

See the poster for more information!

O-180

COLLECTION OF HEMATOPOETIC STEM CELLS
- A NURSING TASK IN AN OUTPATIENT CLINIC.

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Therapy-resistent diseases or relapses have a dismal prognosis and require new treatment modalities. One of the options is high dose chemotherapy with autologous stem cell support. Thus, stem cell collection is a requirement for this therapy.
Using our experience of 270 collections in 57 patients aged 4 months to 30 years, we have established quality standards and working procedures for:
a) choice of steady-state or cytotoxic mobilisation
b) stem cell mobilisation dependent on pretreatment conditions
c) choice of a sufficient venous access
d) clinical and hematological requirements to start a separation
e) individual adjustment of technical parameters to hematological and physiological conditions of the patient
f) priming of the Separator according to the patients's body weight
g) management of fluid, electrolyte and coagulation disturbances

caused by the separation
h) distraction and entertainment for smaller children
i) standard changes if purging is planned
The collection of stem cells in pediatric patients is a very time-consuming and sophisticated job. In order to collect the minimal number of 2 x10^6 CD 34 stem cells /kg body weight for bone marrow recovery, the adherance to certain recommendations is absolutely necessary. Our experience could provide colleagues with such recommendations and thereby help them to do a more efficient job for the benefit of the patients.

O-181

STANDARDS OF CARE FOR PATIENTS RECEIVING HD CHEMOTHERAPY AND STEM CELL TRANSPLANTATIONS.

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Dept. Ped. Hem./Oncology., University of Bonn, FRG

Patients with a prognosis of less than 20% long-term survival in chemotherapy-sensitive diseases receive high dose (HD) chemotherapy with stem cell support in our center in order to improve this prognosis.
31 patients received central venous catheters for the collection of stem cells, which were collected by steady state before or cytotoxic mobilisation during conventional chemotherapy preceeding HD chemotherapy. The three cytotoxic drugs used were VP-16, either carboplatin or ifosfamide, either melphalan or thiotepa which were applied for 5-6 days. Stem cells are returned at day 10 and bone marrow recovery is not expected before day 20.
Nursing prophylaxis and care warrant the success of this experimental therapy. Besides routine nursing care special procedures were developed for therapy-specific problems: exfoliative dermatitis, mucositis, decubital ulcera, cachexia and pain. Infections, bleedings and specific organ toxicities in kidney and lung require additional nursing procedures. Manuals for these complications were developed and are presented.
Trained nursing staff, standards of nursing care and close cooperation with other professionals and the family of our patients are prerequisites of successful management. Since patients with HD chemotherapy and stem cell support are intensive care patients, the nursing staff has major responsibility in this setting.

O-182

AUTOLOGOUS BONE MARROW TRANSPLANTATION IN CHILDREN: NURSING PROBLEMS.

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26 autologous bone marrow transplantations (ABMT) have been carried out in the department of intensive hematology (Tartu University Children`s Hospital) from 1993 to 1997, 11 of them were children. 3 patients with Hodgkin´s disease, 3 with non-Hodgkin´s lymphoma, 1 acute myeloblastic leukemia, 2 acute lymphoblastic leukemia, 1 chronic myelocytic leukemia, 1 with kidney sarcoma have passed transplantation.
We have established follwing pretransplant problems - lack of information about transplantation procedure and possible complications (infections, bleeding); about self protection measures and side effects of medicaments. Posttransplantation status of patients have been influencing nursing profile: susceptibility for infectious processes, mucositis, nutritional demands, bleeding complications; also allergic reactions related to blood component replacement and gastrointestinal problems. Much attention from nursing side have been needing also posttransplant psychological aspects.
In conclusion via individual and high-quality nursing much help can be provided for solution of bone marrow transplantation related problems and therefore patient´s recovery would be facilitated.

O-183

WORK IN PROGRESS - A TWO YEAR EXPERIENCE OF ONCOLOGIC INTENSIVE CARE NURSING IN ST. ANNA CHILDREN`S HOSPITAL

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The Intensive Care Unit (ICU) of St. Anna Children`s Hospital focused on intensive-care oncological patients was founded two years ago. Up to four patients can be provide with artificial respiration in single rooms.
At the hospital about 100 new oncologic patients are admitted every year. About 40 stem-cell transplantations are performed and 10 - 20 patients require intensive care treatment. In former years these patients had to be transfered to ICU`s not specialized on oncological care. Our goal is to grant oncological standards and know-how especially for critically ill patients. Nursing at our ward has to combine standards ICU-care and special hygienic demands typical for transplantation unit.
I would like to exemplify our work on three cases.

O-184

WHAT DO THEY KNOW AND WHAT DO THEY REALLY WANT?

Kei MIYAMOTO, Yoshiko KAJIYAMA
(College of Health Professions, Toho University, Tokyo, Japan)

INTRODUCTION: Pediatric oncology research and treatment has improved remarkably over the past decades. But still, for children who need

unavoidably long hospitalization, there is not enough psychological care in comparison to physical care for children who need . What do they think about their illness? What kind of life and experience do they have in the hospital and what do they really want?
AIM and METHOD: This study is aimed at investigating children's knowledge and concers towards their disease and feelings towards hospitalization and treatments. A total of 9 children aged between 10 to 16, with leukemia, malignant lymphoma, brain tumor and mediastinum tumor, were interviwed using a questionaire.
RESULTS: 1. knowledge of their disease is affected by many factors, i.e age at the onset of illness, frequency of hospitalization, quality of experience in the hospital, education of their parents and family, explanations to the children and their families by physicians and nurses concerning treatments and changes in their daily life.
2. Though some children feel powerless towards their treatments, they themselves take measures to cope with other things that directly affect their daily life. 3. Almost all children usually rely strongly on their family. 4. They strongly want their own will to be respected during hospitalization.
CONCLUSIONS: New approaches to nursing care in pediatric oncology are necessary. All medical personel who take care of hospitalized children should try to understand each individual child. Nurses must see children not only from a disease aspect, but also humanbeings, listen to them carefully, and take time to be with them.

Modern childhood cancer treatment requires a constant balanced cooperation between professionals and parents. The main basis for cooperation is efficient communication. Because keeping day-to-day contact is hardly possible, a form of written communication is offered to professionals and parents: the DIARY.

The DIARY has a triple objective:
1. to optimize the interaction between professionals and parents;
2. to improve the coping strategies of parents
3. to optimize interdisciplinary communication; within the hospital, between hospitals, and between second-line medical care and primary health care.

To achieve these objectives the DIARY contains: treatment protocol, parent-to-parent support and information, room for a log and instructions for: drug administration, the (side) effects of drugs and radiation, central venous system, daily care.
The DIARY is the result of a unique cooperation between professionals of all Pediatric Cancer Units and the Parent Association in the Netherlands.

O-185

INFORMATION VIDEOS FOR CHILDREN WHO ARE TO RECEIVE RADIOTHERAPY

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Patient information material for adults receiving radiotherapy has been well developed and extensively used in clinical practice in recent years. Children under the age of 7 receiving radiotherapy can be informed with the help of drawing and painting books. The age group between 7 and 12 years however lacks specific patient information material. In our hospital concern had grown for children of this age group who developed anxiety and fear when faced with the prospect of having to undergo radiotherapy. These children often had misconceived ideas about what was going to happen to them. Therefore a project was launched, which was financed by "Kom op tegen Kanker" a charitable organisation, to develop specific patient information material and the media video was chosen. The aim of the video was to support the verbal information given by health professionals and to facilitate communication between the child and family members. The different project phases were : literature review on age specific information needs and information processing, developing a video script,production and testing the video. The outcome was the production of 3 different videos, each of 12 minutes long, the 1st intended for children receiving radiotherapy to the brain, the 2nd for children receiving radiotherapy to another part of the body and the 3rd specifically geared to adolescents. In the 1st film emphasis was given to the making of the mask. These films are in current use in our hospital and have been well accepted by both patients and parents. The videos are now being translated for wider distribution.

O-186

THE DIARY: BUILDING A BRIDGE BETWEEN PROFESSIONAL CARE AND PARENTAL CARE

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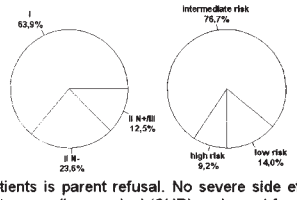
O-187

THE SIOP 93-01 WILMS`TUMOR (WT) TRIAL AND STUDY PROTOCOL. A EUROPEAN UNION CONCERTED ACTION

N Graf, J de Kraker, MF Toumade, B Sandstedt, JMV Burgers, CGM Moorman, H van Tinteren for the SIOP Nephroblastoma Committee (Homburg, Amsterdam, Villejuif, Stockholm)

The treatment strategy of the SIOP 93-01 trial and study protocol is based on the previous results of the SIOP studies. The protocol was started in July 1993. Until October 1996 828 patients (49 % male, 51 % female, mean age 46 mo., median age 37 mo.) from 134 centres out of 15 countries have been registered. 598 patients (72.2 %) are eligible for preoperative chemotherapy. 518 pts. with a localised tumour did receive Actinomycin-D and Vincristine (AV) for 4 weeks and 80 pts. with stage IV disease AV + Anthracyclin° (AVE) for 6 weeks preoperatively. 230 pts. are registered as study patients, mainly because of age (55 pts), primary surgery (88 pts) and stage V disease (57 pts). Tumour volume for eligible pts. with localised disease decreased about 50 % during preoperative chemotherapy (mean volume at diagnosis 465 ml and 286 ml after preoperative chemotherapy). The histological subtype of WT is the most important factor influencing shrinkage of the tumour. **Postoperative treatment for all patients is adapted to different risk groups according to stage and histology.** 252 pts. are eligible for stage I trial. 171 pts. are randomised for two more maintenance courses of AV or no further therapy. The main reason for not randomising eligible patients is parent refusal. No severe side effects of treatment occurred. Preliminary data regarding survival (SUR) and event free survival (EFS) are excellent:



Grouping	N	Event-Free Survival		Overall Survival	
		1 year	2 years	1 year	2 years
Trial	171	87%	85%	100 %	98 %
Protocol	427	87 %	78 %	94 %	92 %
Study	230	86 %	70 %	90 %	84 %
Low risk	67	93 %	93 %	98 %	98 %
Intermediate risk	366	86 %	78 %	99 %	96 %
High risk	44	73 %	56 %	75 %	68 %

Note: November 1996
number of patients at 2 years is rather small, resulting in very large confidence intervals
° *Adriamycin if GPOH, Epirubicin for other centres*
Supported by BIOMED PROGRAMME BMAI-CT94-1147 and Deutsche Krebshilfe T3/95/Gr 2

O-188

A COMPARISON BETWEEN SHORT AND LONG COURSES OF THERAPY FOR WILMS TUMOR. A REPORT FROM THE NATIONAL WILMS TUMOR STUDY GROUP.

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Between 8/16/86 - 9/1/94, 1687 previously untreated children less than 16 years of age with stages I-II/favorable histology (FH) or stage I/focal anaplastic Wilms tumor (WT)("low-risk")(LR) or stages III-IV/FH WT or stages I-IV/clear cell sarcoma of the kidney ("high-risk")(HR) were randomized to receive vincristine and either divided dose ("standard")(STD) courses (5 days) or single dose ("pulse-intensive")(PI) treatment with dactinomycin. HR patients also received either STD courses (3 days) or PI treatment with doxorubicin. Six months after nephrectomy, the 905 with stages II-IV/FH and stages I-IV/CCSK who had not previously relapsed were randomized to either continue chemotherapy for an additional nine months (LONG) or discontinue chemotherapy (SHORT). The two-year relapse free survival (RFS) percentages are shown in the table below.

Regimen	N	RFS	P
Long PI	206	88.9 (± 2.2)	0.74
Short PI	210	87.2 (± 2.4)	0.74
Long STD	205	92.2 (± 1.9)	0.29
Short STD	212	87.7 (±2.3)	0.29

We conclude that LR and HR patients treated with SHORT combination chemotherapy for Wilms tumor have equivalent two-year relapse-free survival to those treated with LONG. We previously reported that PI regimens were as effective as the STD regimens. SHORT PI drug administration is recommended as the new standard.

O-189

WILMS TUMOUR STAGE IV. A REPORT FROM THE SIOP-9 STUDY.

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For the SIOP-Wilms Tumour Committee

Introduction: As has been stated before the stage of the abdominal tumour rather than the presence of haematogenic metastasis at diagnosis plays a decisive role in the outcome of stage IV WT patients.

The Protocol: In SIOP-9 a pretreatment (preop-ct) was given with three drugs (VCR/Act-D/Anthracycl.) for 6 weeks. After nephrectomy subsequent treatment was dictated by the pathological stage of the primary tumour the histological type of the tumour and the status of the metastatic site. Radiotherapy was given in case of abdominal stage II N+ and III or stage >I if unfavourable histology. At the metastatic site RT was only given in case of incomplete resected or inoperable metastasis after nephrectomy. Post-op chemotherapy (ct) was given according to the final grouping of the primary tumour.

Patients: 151 pts were included. Characteristics were: sex ratio 1:1.02, median age 4.66 yrs, bilateral tumours 1.4%, site of metastases: lung 89.6%, liver 15,3%, abdomen 5,5%, bones 2,7%, nodes 2,2%, other 4,1%. Renal tumour stage I: 26,8% II No 26,9% II N+, III 40%.

Results: Information on 150 patients is presently available. There were no events after two years and all patients have a follow-up of more than 2,5 years. EFS is 66.4% with 74.3% of the patients alive. So far 36 children died. Ten of these were anaplastic WT, 3 were clear cell sarcoma of the kidney and 3 were rhabdoid tumours. From these 36, 27% had a stage I abdominal tumour, 29% stage II and 44% stage II N+ and III.

In conclusion: The SIOP strategy including prolonged preop-ct with three drugs, followed by surgery and a postoperative therapy based on stage of primary tumour and remission status at metastatic site, seems to be effective for all sites of metastases. On the other hand the intensity of treatment can be adapted to individual patients to prevent late effects.
(GPOH joined SIOP during SIOP 9)

O-190

SURGERY AS ONLY TREATMENT FOR INSS STAGE 2 NEUROBLASTOMA : SECOND PROGRESS REPORT FROM THE LOCALIZED NEUROBLASTOMA EUROPEAN STUDY GROUP (LNESG) - SIOP 95.01 STUDY.

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In order to evaluate the safety and efficacy of surgery as only treatment in the management of INSS Stage (St) 2 neuroblastoma (NB) without N-*myc* amplification, an European trial is ongoing. Patients (pts) suspected to have a localized NB are registered before surgery. Tumour resectability is evaluated following established radiological guidelines. N-*myc* copy number as well as disease extension evaluation, using INSS criteria, are mandatory. Prospective evaluation of histopathological features (Shimada), serum LDH level, ploidy and 1p deletion are also recommended. Between January 1995 and March 97, 380 pts have been registered from 11 countries with a mean accrual rate of 14 pts/month. Primary localization is abdominal in 60% of the cases and median age at diagnosis is 12 months. In March 1997, data on preoperative evaluation of the risk of primary surgery show at least one risk factor in 146/304 pts, of whom 73/146 will eventually have their tumor removed completely (50) or grossly (23) without prior chemotherapy. Data on Stage are available on 261 pts with NB (104 St 1, 22 St 2A, 41 St 2B, 88 St 3 and 6 St 4 or 4S). In addition, 25 Ganglioneuroma are observed. Only 52 St 2 pts with NB are eligible in the trial and median follow-up is 9 months (0 to 28). Eleven relapses have occurred 1 to 10 months after surgery : 11/11 in the primary tumour site or regional lymph nodes and 5/11 in distant sites. One pt died of disease progression 13 months after surgery. Considering the St 1-2 population (without N-*myc* amplification) treated by primary surgery only the factors favouring relapse are St 2 v. St 1 (p= 0.015), and abnormal v. normal LDH plasma level (p=0.0035). Data on possible influence of histology, ploidy and 1p deletion on relapse will be presented. These preliminary data confirm the importance of careful prospective studies for children with localized NB.

O-191

ALVEOLAR SOFT PART SARCOMA (ASPS) IN CHILDREN AND ADOLESCENTS. THE EXPERIENCE OF THE INTERNATIONAL SOCIETY OF PEDIATRIC ONCOLOGY (SIOP).

Sommelet D*, Devalck C, Oberlin O, Rodary C, Dowell HMc, Foot A, Sanchez de Toledo J, Terrier-Lacombe MJ, Spicer R, Quintana E, Flamant F, Stevens MCG, on behalf of SIOP MMT Committee, *Children's Hospital, Nancy, France

In adults, ASPS described by Christopherson is very rare and surgical resection remains the mainstay of therapy. The survival rate is around 40% at 10 years, due to local and mainly metastatic relapses occuring tardily. In children, the prognosis may be more favorable.

Material and methods : From 1984 to 1995, 12 ASPS (4.5%) out of 271 non rhabdo malignant mesenchymal tumors (MMT) were enrolled in 2 consecutive studies conducted by the SIOP for non rhabdo MMT. Mean age : 11 years

(range 3 to 13.5 yrs) ; sex ratio : 5 M/6 F. Primary sites were located in limbs (6), head and neck (5), abdominal wall (1). 4 tumors were larger than 5 cm at diagnosis. According to TNM staging, 9 were stage I, 1 stage II and 2 stage IV. Initial resection was complete in 5 pts (3 pT1, 2 pT2) and microscopically incomplete in 3 pts (pT3a) : 4 pts underwent only biopsy or macroscopically partial resection (pT3b). All pts received multiagent chemotherapy (CT), either as adjuvant in 5 pts or neoadjuvant in 7 pts (1st line : Ifo/VCR/Actino ; 2nd line : CDDP/DXR or VM26/DXR/Carbo).

Results : In 10/10 localized ASPS, local control was achieved by complete surgery (S) in 4 pts (1 of them was irradiated), by incomplete S and CT in 3 (pT3a), CT and RT in 3 (pT3b). **9/10 pts are alive in continuous complete remission** (median follow-up of 60 months). One patient previously treated by 6 IVA after complete S, developed a distant metastase and is alive 5 months later. Two pts had lung metastases at diagnosis. One of them is alive and disease-free 40 months later.

Conclusion : 1) Despite the small number of pts in that series, we confirm the better outcome of ASPS in childhood. 2) The potential value of CT has to be confirmed ; however 3 pts are in 1st CR after incomplete S and CT, while one metastatic pt remains disease-free.

Supported by Association pour la Recherche sur le Cancer.

O-192

NON METASTATIC SYNOVIALOSARCOMAS (SS) IN CHILDHOOD AND ADOLESCENCE. THE EXPERIENCE OF THE INTERNATIONAL SOCIETY OF PEDIATRIC ONCOLOGY (SIOP)

Sommelet D*, Aguercif F, Oberlin O, Rey A, Terrier-Lacombe MJ, Godzinski J, Calvo C, Stevens MCG, on behalf of SIOP MMT Committee, *Children's Hospital, Nancy, France

In adults, SS are defined by a high rate of local and mainly metastatic relapses (50%) ; in spite of their chemosensitivity to neoadjuvant chemotherapy (CT), the survival rate has not been influenced by adjuvant CT. In childhood, SS may have a better prognosis.

Material and methods : 42 patients (pts) with SS were registered from 1984 to 1995 in 2 consecutives studies for malignant mesenchymal tumors (MMT 84 and MMT 89), representing 15.5% of the non rhabdo MMT. 39 SS were localized. Sex ratio : 1. Mean age : 11 yrs (4-16.5). Primary sites was : limbs (30), neck and trunk (9). Tumor size was more than 5 cm in 62% of cases. According to the TNM staging, 23 SS were stage I and 16 stage II. Initial surgery (S) was complete in 9 pts who received adjuvant CT ; S was partial in 30 pts, with a microscopic residue in 12 pts (pT3a) and a macroscopic residue in 18 pts (pT3b) ; these 30 pts received primary CT (1st line : Ifo/VCR/Actino ; 2nd line : CDDP/DXR or VM26/DXR/Carbo) with the objective to perform a conservative S and to deliver radiotherapy (RT) only on macroscopic residue.

Results : Complete remission (CR) was obtained in 37/39 pts (95%) : by complete S (9 pT1T2) or after incomplete S by : CT alone (9 pT3a, 1 pT3b), CT + 2nd S (1 pT3a, 9 pT3b), CT + RT (2 pT3a, 4 pT3b), CT + 2nd S + RT (2 pt3b). 11/37 pts (30%) relapsed : 8 local, 2 metastatic, 1 both. Before relapsing, these pts have been treated by complete S (4), S with microscopic residue + CT (4), S with macroscopic residue + CT + 2nd S (2) and CT + RT (1). **34/39 pts are alive (87%) : 26 in 1st CR, 8 in 2nd CR.** 5 pts died : progressive initial disease (2), metastases (3). The only unfavorable prognostic factor is the stage II ($p < 0.0001$). 5 out of 14 pts evaluable pts (36%) were responding to CT (1 CR and 4 PR).

Conclusion : 1) We confirm that SS prognosis appears more favorable in children than adults. 2) A conservative approach (3 amputations and 8 irradiated pts/39 pts) does not jeopardize the survival rate. 3) A second long-term CR is observed in 8/11 pts.

Supported by Association pour la Recherche sur le Cancer.

O-193

CONSERVATIVE TREATMENT OF NON METASTATIC MALIGNANT MESENCHYMAL TUMORS (MMT) OF THE GENITAL TRACT IN FEMALES A SIOP MMT 84 + 89 STUDY

Martelli H, Godzinski J, Spicer RD, Habrand JL, Haie-Meder C, Rey A, Praquin MT, Calvo C, Oberlin O, Stevens MCG - For the SIOP MMT Committee.

From 1984 to 1994, 40 girls with MMT of the genital tract have been treated according to SIOP MMT 84 and 89 protocols. **Histology** was RMS in 38 cases (2 alveolar), spindle cell sarcoma in 1 and embryonal sarcoma in 1. **Localisation** of the primary tumor was vagina and/or vulva in 28 pts (70%) and uterus in 12 (8 cervix, 4 uterine corpus-5 extension to vagina). **Median age** was 25,5 m. (9 m-16,5 years), uterine tumors beeing older (12 years) than vaginal tumors (22 m.). The 5-year **survival rate** is 93% (75-98%) and 5 year **DFS** is 79% (61-89%). **Stage and treatment** : 4 girls had complete resection at diagnosis; among 36 pts with incomplete resection or only biopsy at diagnosis, 25 were stage I, 10 stage II and 1 stage III. After initial CT (Ifo-VCR-Actino), 24 pts had a complete clinical response (13 biopsies of the tumor bed with 4 positive T cells found), 11 need a local treatment for a residual mass and 1 progressed.**Results : Two pts died,** 1 alveolar stage III RMS after locoregional relapse and 1 who never achieved complete remission (CR). **Thirty-eight girls are alive** with a median FU of 45 m. (10-110 m.), 33 in first CR and 5 in second CR:

- 4 pts with a microscopically complete resection at diagnosis (1 vaginal tumorectomy - 3 wedge excision of cervix) and 2 courses of VCR-Actino are alive with 14,53,60 and 67 m. FU.
- 15 girls (39%) received CT alone (14 are in first CR with a median FU of 26 m., 1 is in second CR but lost for FU 6 m. after relapse).
- 19 pts (50%) underwent a local treatment for a residual mass after initial CT (11), for tumor cells on biopsy (3), for relapse (4) and for spindle cell sarcoma (1). Local treatment was radiotherapy (RT) in 10 pts (7 BrachyT, 3 external RT) , radical surgery (RS) in 5 pts (4 hysterectomy, 1 total vaginectomy), RS + RT in 2 pts and conservative surgery in only 2 pts (1 tumorectomy + RT, 1 partial vaginectomy).

Conclusion : Vaginal and uterine tumors have the same good prognosis but corpus tumors may need hysterectomy to be cured. One third of the pts have been cured by CT alone, without local treatment. Conservative surgery seems very difficult in this site and intravaginal brachyT, in spite of possible late sequelae, seems the local treatment of choice.

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PROGRESS IN THE TREATMENT OF NON METASTATIC RHABDOMYOSARCOMA: A REPORT FROM THE SIOP MMT COMMITTEE

MCG Stevens, O Oberlin, J Sanchez de Toledo, A Rey for the SIOP MMT Committee.

MMT95, the fourth SIOP soft tissue sarcoma study, opened in July 1995. The concept developed from lessons learned from studies commencing with RMS 75 (Radiother. Oncol. 1985, 3, 227-236). Overall survival (OS) was poor (40% at 3yr) but the results suggested the value of initial chemotherapy (CT) in limiting the extent of local therapy for patients with residual/unresectable disease at diagnosis.

MMT84 sought to explore intensified initial CT utilising Ifos. Vcr. ActD. (IVA) to reduce or avoid local therapy. Complete remission (CR) was achieved with CT alone in 48% patients. Patients achieving CR with CT +/- Surgery (S) did not receive local treatment (depending on site). 5yr OS was 66% and < 40% patients received local therapy (S +/- RT). Excluding those with PM disease, only 26% received RT as part of primary treatment.

MMT89 refined treatment by prognostic group (defined by site and stage). Localised completely resected tumours (IpT1) were treated without alkylating agents (87% 5 yr. OS). Intensified IVA (9g Ifos/m2/course) made no impact on 5 yr. OS (71%) but the use of an intensified 6 drug regimen (IVA + Carbo, Epiadr, Etop, initially used for metastatic disease) improved survival in Stage III (N1) patients. (57% 5 yr. OS vs. 42% in MMT 84). This formed the basis of a randomised study structure (IVA vs. 6 drugs) in MMT 95. The randomisation applies to selected groups of patients with less favourable disease and local treatment still depends on site and response to initial CT.

Other major objectives for MMT95 are to maintain OS but improve DFS for stage IpT1 patients by using the same limited CT strategy but more precise pre-treatment staging and pathological assessment; and to confirm the improved outcome for Stage III patients using 3 cycles (9 courses) of the 6 drug CT strategy. By December 1996, 194 patients. had been registered on study of whom 96 were randomised. Recruitment to the SIOP MMT studies has extended beyond Europe, including centres in Argentina and New Zealand. The results of MMT95 will be analysed in parallel with the current German/Italian Co-operative study which also explores the value of the 6 drug schedule in randomisation with previous conventional therapy.

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SIOPEL 2 PILOT STUDY ON CHILDHOOD HEPATOBLASTOMA (HB) PRELIMINARY DATA - A SIOP LIVER TUMOUR STUDY GROUP TRIAL

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The aim of the study was to test efficacy (tumour response/resectability rate) and acute toxicity of two new chemotherapy (CT) regimens and to compare these with the CT (PLADO) used in SIOPEL 1, before launching the next trial. The eligibility criteria were: age 0-16 years, no previous treatment and histologic diagnosis. Tumours were staged with abdominal US, ± CAT scan, ± MR; chest X Ray (PA/LL) ± chest CAT scan; serum α-FP. Pre treatment Tumour Extension (PRETEXT) was assessed according to the number of liver sector free of tumour, PRETEXT I-IV, and presence of metastases (M), involvement of vena cava (V) and extra hepatic extension (E), (0 absent + present). Pre-operative CT was the rule. Assignment to the two CT regimens was according to risk categories. Low risk (LR) defined as PRETEXT I-III, with no (0) M, V, E. High risk (HR) defined as either PRETEXT IV, or positive (+) M, V, E; or both of any combination. LR pts were treated with Cisplatin (CDDP) 80 mg/m^2/d q15 days and the tumour was assessed for resectabilty after 4 to 6 courses. HR pts received Carboplatin 550 mg/m^2/d1; Doxorubicin 60 mg/m^2/d 2-3 in 48 hr c.i., CDDP as per above d 15; CT was administered every 15 days and tumour resectabilty was assessed at days +85 or +115. Stopping rules were set according to the SIOPEL 1 data. Response was assessed according to fall of α-FP and tumour shrinkage. Results from 9/95 to 12/96 60 pts, (27 females - median aged 12 months) have been registered in the study from 17 nations throughout the world; 37 from Europe, 15 from South America, 7 from Oceania and 1 from Asia. 35 were LR and 25 HR; Pt distribution by PRETEXT was PRETEXT I 1, II 16, III 11, IV 5, unknown 27; 7 pts were M+, 32 M 0 (data missing - 21). As of 2/97, treatment results are not for publication yet. Conclusions: recruitment rate exceeded expectations; if the stopping rules are not met before the next interim analyses pt recruitment will continue until activation of the main trial.

O-196

Lessons learnt from the First International Prospective SIOP Trial (SIOPEL I) for Hepatoblastoma (HB) and Hepatocellular Carcinoma (HC) in children.

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The **primary aim** of the study (Jan 1990 - Feb 1994) was to investigate the feasability efficacy and outcome of a new strategy using PRE-OPERATIVE chemotherapy (CT) in all children (0-16 years) with verified Hepatoblastoma (HB) or Hepatocellular Carcinoma (HC). 154 cases of HB and 40 of HC were registered in 30 countries.
The **methods** have been previously reported*. Instead of updating the **results*** which are essentially similar to those reported last year, we would like to point out some salient observations crucial to planning SIOPEL II Pilot and SIOPEL III. A full update is in publication.
Lessons learnt for Hepatoblastoma
Preoperative chemotherapy (PLADO) is feasable with acceptable toxicity (3 deaths, 2 in malnourished children and only 29 dose reductions in 766 courses) and appears to be less than a study in the USA with similar but not exactly equivalent CT regimen.**
The Primary resectability rate after chemotherapy is high (76%) with less unsucessful attempts at resection (10%). The local recurrence rate very low (4%).
A rapid central review panel is essential in equivocal cases, to decide on resectabiliy.
Liver Surgery should only be performed in appropriate designated centres to reduce surgical complications (5 deaths). **Liver Transplantation** is a very reasonable option in PRETEXT 4 or multifocal disease if response to chemotherapy is good (9 out of 13 ANED) and should be carried out early on.
Good concordance of pathological diagnosis with central review obviates the need for central review as far as treatment is concerned.
Metastatic patients (20%) have done better than in other series (OS 62%, EFS 32%) (Early exposure to CT?), but have had alternative therapy. **High** and **Low Risk Groups** have been identified and will have risk adjusted treatment in SIOPEL II and III).
Registration procedures and forms need to be streamlined and simplified.
HCC requires a different treatment strategy to Hepatoblastoma. SIOPEL I has demonstrated that international co-operation in rare tumours can be successful in spite of inherent logistic problems.

SL-1

WHY LOOK AT RETINOBLASTOMA IN DEVELOPING COUNTRIES AS A POTENTIALLY UNIQUE DISEASE?

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We have described an increased relative frequency of retinoblastoma in southern India [Schultz *et. al.* Cancer 72(1):282-286, 1993]. More recently, we observed a similar increased relative frequency in South African blacks [Strahlendorf C, et. al. "Retinoblastoma: An increased relative frequency in South Africa" ASPHO 1995]. Other groups have also suggested an increased relative frequency of retinoblastoma in some developing countries of the world. Our analysis of the South African data also reveals that the children are being diagnosed at relatively similar ages to children in developed countries, but with a much higher frequency of metastatic disease at diagnosis and large tumors at the primary site. Response to therapy is quite poor. These findings have lead us to hypothesize that 1).the incidence of retinoblastoma appears to be increased in developing countries; 2). the disease presents more aggressively than retinoblastoma in developed countries; 3). these children are more refractory to usual retinoblastoma therapy; and 4). retinoblastoma in developing countries may represent a distinct subtype of retinoblastoma from that seen in developed countries. I also hypothesize that there may be unique etiologic factors causing an increased incidence of retinoblastoma. Possible agents may be a lack of vitamin A or folate in the diet or increased exposure to Adenovirus or Papilloma virus. I propose that we consider organization of Pediatric Oncologists in developing countries to begin to confirm or refute whether there is an increased incidence of retinoblastoma in developing countries and begin to explore for possible etiologies and improved therapies.

SL-2

RETINOBLASTOMA IN A DEVELOPING COUNTRY: THE CHALLENGE OF EARLY DIAGNOSIS

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Retinoblastoma has an annual incidence of around 3-5 per million. One of the highest rates is reported for Brazil. Disease stage is the most important variable in prognosis. When disease is confined to the globe, i.e., intraocular retinoblastoma there is a better prognosis than when disease spreads beyond the globe. From 1975 to 1994, 378 patients with retinoblastoma were referred to the Pediatric Department of A.C. Camargo Hospital. Frequency distribution by extension of disease was during the period: 1975-1985 - (153 cases) 43.8% intraocular disease (IO) versus 56.2% extraocular disease (EO); the period 1986-1990- (105 cases) 75.2% IO vs. 24.8% EO; and the period; 1991-1994 (120 cases) 75.8% IO vs. 24.2% EO, differing significantly between the first vs. the second and third ($p<0.000$). Eighty (52.3%) cases were early referral (admitted before 6 months from onset of symptoms and treatment) during the first period vs. 75 (75%) during the third period. The frequency of bilateral and unilateral disease was similar in all periods. The shift in disease extension distribution was associated with early referral. During the third period 47.5% were referred less than 3 months from the onset of symptoms and treatment vs. 47.7% referred more than 6 months during the first period. Clinical after onset stage and lateness of referral were strongly associated with the overall survival. In 1986 we instituted a program to change the incidence of advanced stages in our country. Professional groups were approached through articles in regional medical journals, lectures, and the formation of a cooperative study group. Lay people were reached through advertisement in outdoor, newspaper, and television and lectures in primary schools. This campaign, and creation of a multi-disciplinary team were responsible for early referral and improved survival.

SL-3

RELATIVE FREQUENCY AND TREATMENT OF RETINOBLASTOMA IN JOHANNESBURG, SOUTH AFRICA: A NEW VISION FOR DEVELOPING COUNTRIES

Caron Strahlendorf, University of Witwatersrand, and The Chris Hani Baragwanath Hospital, Soweto, South Africa.

In developing countries Retinoblastoma (RBL) may account for as much as 15% of paediatric oncology cases, compared to the reported incidence of 3% in developed countries. True incidence data is difficult to establish in developing countries. This study therefore used the relative frequency of RBL in black children treated at a single institution in South Africa. Of the 600 children seen with malignancy from 1989 - 1996, 94 (15.6%) had histologically confirmed RBL. Thirty-one percent had bilateral disease, and both unilateral and bilateral cases presented at an older mean age than that reported in Western centres. UICC and SEER data was used to compare the ratios of RBL, Wilms, and Neuroblastoma. This confirmed the conclusion that the relative frequency of RBL was increased. Eight-four percent of RBL patients had disease not amenable to conservative therapy and 32% had metastatic disease (standard staging). The response to adjuvant chemotherapy (VEC)in extra-orbital RBL was evaluated. Chemotherapy was well tolerated, with minimal toxicity. The overall survival was 44%, probably reflecting advanced disease. Seven percent of cytogenetics were abnormal. Of 5 tumours which had molecular genetic analysis using SSCP, 3 were somatic and 2 germline. The following recommendations are made:

1. Culturally appropriate education (to avoid late presentation);
2. Explore the possibility of a different disease;
3. Uniform staging is required;
4. Multicentered protocols are need to improve DFS;
5. Treat as outpatients aiming for minimal toxicity;
6. Recognize limited financial resources;
7. New agents should be explored.

SL-4

Is retinoblastoma in developing countries a distinct subtype of retinoblastoma?

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Retinoblastoma accounts for approximately 3% of paediatric malignancies in developed countries, and occurs in both a hereditary and non-hereditary form. Variations in the rates of retinoblastoma in different parts of the world suggest either different reporting patterns or a true difference in risk among different populations. A difference in risk may be related either to genetic or environmental factors, with an increased proportion of unilateral cases and/or changes in incidence over time suggestive of possible environmental influences. However, it is difficult to determine the incidence rate of retinoblastoma in many developing countries, due to the lack of population-based statistics.

Reported retinoblastoma incidence from the publication International Incidence of Childhood Cancer (Parkin DM et al. International Incidence of Childhood Cancer. IARC Scientific Publication No 87, Lyon, 1988) among US white children aged 0-14 years in the 1980's is 4.0 per million. Data in this publication suggest that retinoblastoma is more frequent in parts of the Indian subcontinent, South America and Africa. Other studies from Africa, India, and non-white populations in the US showed increased rates in these groups, and changes in incidence over time. Parkin DM and colleagues reviewed childhood cancer rates in developing countries and suggested that viral infection may be a risk factor for retinoblastoma, based on geographic and ethnic patterns of incidence (Environmental Factors Int J Ped Hem/Onc 2(5):411-417, 1995).

In order to further investigate the influences of genetic and environmental factors for this disease worldwide, there is a need to obtain population-based incidence data and information on the proportions of unilateral and bilateral cases from more countries and ethnic groups. Studies of relative frequency are insufficient in that variations in incidence and reporting completeness of other tumours bias results. Investigations of migrant populations and information on changing incidence over time will also help to determine the factors responsible for the differences in incidence of retinoblastoma around the world.

SL-5

COLLABORATIVE PROJECTS OF RETINOBLASTOMA THERAPY IN DEVELOPING COUNTRIES: INITIAL EXPERIENCES IN INDIA.

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Our interest in developing a collaborative project for treatment of retinoblastoma (RB) originated from three observations; 1) Schultz et. al. (Cancer 1993, 72:782) confirmed earlier observations that the incidence of RB may indeed be high in the Indian subcontinent; 2) RB cases constitute a high fraction of cases at major pediatric cancer facilities in India (private communication Drs. Arya and Advani); and 3) initial experience with neoadjuvant chemotherapy in germline RB suggests that external beam radiation (EBR) and/or enucleation (ENC) can be avoided in a significant number of cases (Taub et. al proceedings SIOP 1995). The above suggested that a collaborative project could be developed a) to initiate a multi-disciplinary approach to treatment of RB in India (and other developing countries) and 2) the high incidence of RB in India would lend itself to the development of novel therapeutic approaches aimed at preservation of vision and avoid enucleation. We hypothesized that the social stigma associated with a genetic disease and the physical defect of enucleation are some of the reasons for delaying appropriate care and hence the high frequency of advanced stage extraorbital disease. An exploratory visit to India in April 96 and the following issues were identified a) RB indeed constitutes a large fraction of he oncology diagnoses encountered in major centers (nearly 90 new cases each year at RP Eye Institute in New Delhi); b) argon laser and cryotherapy facilities (essential for local therapy of small lesions) are available in major centers; and c) most importantly there is genuine interest in developing a multidisciplinary approach to management of RB in the major centers. A follow-up visit is planned for the fall of 1997. Major issues to be addressed are: 1) familiarize ophthalmologists with criteria for local response after local therapy and 2) the costs of chemotherapy.

SL-6

NEW DRUG DEVELOPMENT IN PEDIATRIC ONCOLOGY IN FRANCE

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New active drugs and therapeutic strategies are needed to further improve the efficacy of cancer treatment in several diseases such as neuroblastoma and brain tumors, and to decrease the short and/or long term complications. In 1986, the SFOP embarked on the evaluation of new drugs and drug combinations in phase II studies in pediatric malignant solid tumors. For example, this programm identified the high activity of VP-16 Carboplatin combinations in neuroblastomas, medulloblastomas and Wilms' tumors. In parallel, great efforts were made to provide the investigators with comprehensive Methodology Guidelines for Phase II trials. These were discussed within the SIOP and, later on, recognized as the Official SIOP Guidelines by the Scientific Committee. In 1992, the need to develop phase I studies of new drugs which were in current development in adults and not yet licensed (taxoids, topoisomerase I inhibitors,....) became obvious. The SFOP Pharmacology Group was created to promote new drug development and clinical pharmacology studies in pediatric oncology. This group is composed of pediatric oncologists and pharmacology researchers. However, new anticancer drugs for pediatric studies are particularly difficult to get from Pharmaceutical Companies, especially in Europe. In order to provide a preclinical rationale for the choice of new agents to study, a new panel of pediatric tumor xenografts, mainly brain tumors and neuroblastomas, was established at the Institut Gustave Roussy, Villejuif. This panel has yet identified topoisomerase I inhibitors as potentially active drugs. In the last 2 years, a phase I study of paclitaxel (Taxol®) given as a 3-hour i.v. infusion was conducted in France : neurotoxicity was dose-limiting. A phase I study of irinotecan (Campto®) given as a 2-hour i.v. infusion was initiated. In 1995, the GP-SFOP and the New Agent Group (NAG) of the UKCCSG decided to collaborate in order to promote more efficiently new drug development in pediatric oncology. During the last 2 years, 2 joint studies have already been initiated : a phase I study of PSC833 (a mdr revertant drug) in combination with VP-16 and a phase II study of Temozolomide (Temodal®) in malignant glial brain tumors. In the next future, the two groups will increase their collaboration. Indeed, new cytotoxic drugs are currently in clinical development in adults (new antifolates, new antipurines, new topoisomerase I inhibitors,.....). Many new potential targets for cancer treatment, such as cell differenciation pathways, gene expression and angiogenesis, are being intensively investigated. The GP-SFOP and the NAG-UKCCSG strongly believe that their collaboration will contribute to develop new active drugs in pediatric oncology in accordance with the Good Clinical Practice regulations.

SL-7

PHASE 1 STUDY OF IRINOTECAN (CPT-11) IN CHILDREN WITH ADVANCED NEUROBLASTOMA.

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Irinotecan, a camptothecin derivative, is a novel anti-cancer agent developed in Japan, acting as a specific DNA topoisomerase I inhibitor. Experimental studies using human neuroblastoma xenografts disclosed that it could be a promising chemotherapeutic agent against human neuroblastoma in advanced stages. A phase I study of CPT-11 is being conducted in Japan in children with advanced neuroblastoma who had recurrence of tumor or who failed to become in remission after intensive induction chemotherapy with the regimens of the Study Group of Japan. CPT-11 was administered as a 120 min i.v. infusion for 3 consecutive days every 4 weeks, starting at 50 mg/m²/day dose level with 10 mg/m²/day dose escalation. So far 22 patients had recurrent or refractory neuroblastoma and were enrolled, but 21 of the 22 are evaluable. Their median age was 6.8 yr (3 yr-12 yr); sex ratio M/F, 7/14; performance status, 0-1.

Dose(mg/m²)	50x3	60x3	70x3	80x3	90x3	100x3	110x3
no. of pts	2	3	4	4	4	3	1
NCI grade	~2 3 4	~2 3 4	~2 3 4	~2 3 4	~2 3 4	~2 3 4	~2 3 4
Leukocytes	2 0 0	3 0 0	3 1 0	4 0 0	3 0 1	2 1 0	1 0 0
Diarrhea	1 0 1	3 0 0	4 0 0	4 0 0	4 0 0	2 1 0	1 0 0
Vomiting	1 0 1	3 0 0	3 1 0	4 0 0	4 0 0	2 1 0	0 1 0

Toxicities other than myelosuppression and gastrointestinal symptoms were observed in one patient who showed grade 2 lower leg pain. One patient was dropped out after one cyclic administration of CPT-11, 70mg/m²/day because of nausea and vomiting. Two partial response and 18 stable disease were observed among 21 evaluable patients; response is not determined yet in the last patient. At present no dose limiting toxicity was observed in 3 patients at 3 days administration of 100 mg/m²/day. Profiles of serum concentrations of CPT-11 and SN-38 were also measured in these patients.
Conclusion: dose limiting toxicity is not yet achieved at the dose of 100 mg/m²/day for 3 consecutive days. Final results and phamacological data will be presented.

SL-8

CHEMOTHERAPY AND MIBG UPTAKE IN NEUROBLASTOMA CELL LINES.

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